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IN

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MODERN TRENDS

IN

GASTRO-ENTEROLOGY

Edited by

F AVERY JONES

M D F R C P

PHYSICIAN CENTRAL MIDDLESEX HOSPITAL CONSULTANT IN GASTRO-ENTEROLOGY TO THE POSTGRADUATE MEDICAL SCHOOL OF LONDON TO ST MARK S HOSPITAL AND TO THE ROYAL NAVY

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FOREWORD

THE TERRITORY OF GASTRO-ENTEROLOGY is so vast and so varied that its frontiers have hitherto defied any exact delimitation nor has any narrow national allegiance been demanded of its colonists Physicians and surgeons psychologists and endocrinologists physiologists anatomists histologists biologists and bio chemists have all entered its domains some as explorers some in transit some as settlers but all as is the way of human kind tending to cultivate their own plot in their own way without study of the crops that are being garnered on neighbouring properties and all turning for companionship to clubs and societies patronized by like minded individuals who have the same background and who speak the same language

Wise men have lamented that the difficulties of the clinician may be unknown outside the wards while the discoveries of the scientist that might provide the answer remain a secret of the laboratory This lack of diffusion of knowledge is an almost inevitable sequel of the increasing pace of the advance of knowledge In any form of travel the faster we go the more is our vision limited to a narrow cone directly ahead the less do we see of what is going on above below and on each side of our path of advance Research moving with increasing accelera tion has become a matter of organized effort in which each member of a team undertakes some small aspect of an inquiry of whose general scope he may be ignorant describes his discoveries in technical jargon and alphabetical abbrevia tions and publishes his results in a trade journal circulating only among the fraternity Research is not in itself a secret cult The word means no more than constant inquiry and inquiry alone can seldom lead to advance unless the sectional answers obtained by individuals are integrated into a larger whole It is humiliating to think that many of the problems outstanding today might be solved if only the pieces of the answer which lie in obscure volumes on dusty shelves could be assembled and fitted together by someone with the trained vision to see and the leisure to sit down and think

Dr Avery Jones has done a great service to gastro-enterology and to British medicine in planning this book and carrying it to fruition In it he has assembled the latest and the best work in many related fields and what is perhaps equally important he has omitted those aspects in which no advance has been made in recent years in order to devote more space to the really important work in a volume of manageable (and purchasable) size Physicians and surgeons perhaps more than any of the many classes of reader to whom the book will appeal will welcome it for the clear presentation it gives of work that they would otherwise never encounter outside the pages of the *Quarterly Journal of Medicine* or the *British Journal of Surgery* Both will be grateful for the masterly articles dealing with the scientific basis on which modern gastro-enterology rests

Above all this work is a credit to British medical science since it brings together for the first time a great body of original work of the utmost importance in a form in which it can be understood and appreciated by the non specialized reader

HENEAGE OGILVIE

London 1952

INTRODUCTION

THE PURPOSE OF THIS BOOK is to bring together recent work in the gastro-entero logical aspects of medicine and surgery In many countries as in Great Britain gastro-enterology is not an established speciality such as cardiology or neurology but remains within the sphere of general medicine and surgery This book is therefore not written only for gastro-enterologists but for physicians and surgeons interested in this field Each section has been undertaken by someone who has made a recent contribution to the particular subject for such contributors are best able to present an up to-date account of their subject with recent progress given its correct perspective

Even with a large volume it is not possible to give space to every aspect of the subject and it makes no claim to be completely comprehensive Those fields in which there has been most progress are best represented as for example the oesophagus liver diseases and peptic ulcer

Gastro-enterology has a greater number of unsolved aetiological problems than any other system of the body In addition to bringing together modern knowledge an attempt has been made also to represent growing points of research from which important clues may be contributed to major unsolved problems such as peptic ulcer For example the mechanism of secretion of acid by the stomach and vascular anatomy of the stomach are not sections with such intrinsic appeal to the clinician as the anaemias of the alimentary tract Nevertheless they present recent work which may prove of great importance There is a particular need for more research workers to be attracted to gastro-enterology and it is hoped that this publication may have some influence in this direction

Close collaboration between physicians and surgeons is particularly needed in gastro-enterology and this is well reflected in the list of contributors The application of existing knowledge to the practical management of for example ulcerative colitis is possible only if physicians and surgeons are willing to work together preferably leaving the patient in one ward No apology is offered for introducing some details of surgical technique where it has been thought desirable It is hoped that thereby the surgical reader may be given valuable practical points not readily available elsewhere and it is not without interest for the physician to have some impression of modern surgical methods

This publication is essentially representative of British and Australian work in gastro-enterology Much valuable work has been done in recent years in America where gastro-enterology has clearly been separated from general medicine and surgery as a distinct speciality Such American work has however been adequately brought together in recent publications and has been more readily available hitherto than corresponding British work

I wish to express my best thanks to the Medical Department of Messrs Butter worth & Co for the great help they have given me

F AVERY JONES

London 1952

CHAPTER 1

ANAEMIAS OF THE ALIMENTARY TRACT

L J WITTS

THE BODY responds to anaemia by speeding up the circulation and increasing the extraction of oxygen from the haemoglobin in the red cells This compensation is usually adequate as far as the digestive organs are concerned and we need not spend time in discussing the effects of anaemia *per se* on the alimentary tract We have to concern ourselves with the changes which take place in the alimentary canal in the primary diseases of the blood more particularly the anaemias due to deficiency of haemopoietic factors or dyshaemopoietic anaemias the blastomatous disorders such as leukaemia and Hodgkin s disease and the haemorrhagic diseases

THE DYSHAEMOPOIETIC ANAEMIAS

The chief deficiencies which give rise to anaemia are deficiencies of iron and the liver principle The most important example of iron-deficiency anaemia is the chronic hypochromic anaemia which occurs characteristically in women during the reproductive period of life The anaemia is of low colour index with a low mean corpuscular haemoglobin and less constantly microcytosis The serum iron is low Factors usually responsible are diminished intake of foods containing iron impaired absorption of iron and increased loss of blood Chronic hypochromic anaemia shades indefinitely into chronic haemorrhagic anaemia but the anaemia seems out of proportion to the loss of blood and associated symptoms such as koilonychia splenomegaly and alimentary changes contribute to a characteristic clinical picture

The anaemias due to deficiency of the liver principle form a more complex group and the single unifying factor is the presence of megaloblastic degeneration of the bone marrow Although it is convenient to speak of the liver principle two quite distinct chemical substances have now been isolated vitamin B_{12} and folic acid It appears that vitamin B_{12} and folic acid participate in enzyme systems as yet imperfectly elucidated which are concerned with the growth of cells and the integrity of nervous tissue It is possible to arrange the megaloblastic anaemias according to their response to these two haemopoietic factors in a spectrum with pernicious anaemia at the one end and achrestic anaemia at the other In between come pernicious anaemia of pregnancy megaloblastic anaemia of infancy nutritional macrocytic anaemia and the various forms of steatorrhoea and intestinal macrocytic anaemia Pernicious anaemia responds completely to vitamin B_{12} and inadequately to folic acid Achrestic anaemia responds completely to folic acid

tract is sensitive to nutritional deficiencies which impair the constant replacement of cells which is normally taking place These deficiencies may be dietary they may be conditioned by a fault in the alimentary tract or they may be the result of increased metabolism Any attempt to allocate lesions exclusively to one aetiological factor is to some extent schematic as deficiencies are commonly multiple Nevertheless the appearances are often sufficiently distinct to allow the deficiencies to be differentiated clinically and the effects of treatment are specific The buccal lesions of iron deficiency occur only when the serum iron is low they do not respond to vitamins and they are healed by treatment with iron The glossitis of pernicious anaemia responds well to vitamin B_{12} less well to folic acid and not at all to other vitamins or iron In pernicious anaemia of pregnancy vitamin B_{12} cures the glossitis even though folic acid may be necessary for the cure of the anaemia (Ginsberg and others 1950) The scheme given in Table I is a modification of one devised by Waldenström (1941)



FIG 1 —Atrophic glossitis and unusually extensive angular stomatitis (woman 44 years) This woman had brittle nails hypochromic anaemia serum iron 13 micrograms per cent normal gastric acidity and pruritus vulvae of long standing which had resisted local treatment All symptoms were relieved by treatment with ferrous sulphate by mouth

Oral lesions

The angular stomatitis of iron deficiency is characterized by soreness and cracking of the skin at the corners of the mouth (Fig 1) extending about 1 centimetre on to the cheek Crusting is unusual and the lesion may not be seen when the mouth is closed Healing of the fissures may leave small scars at the corners of the mouth and there may be wrinkling of the skin round the mouth which is probably not entirely explained by loss of teeth but is due also to atrophy of the tissues Angular stomatitis of the same type may occur in pernicious anaemia but less frequently

Glossitis on the other hand is more constant in pernicious anaemia Wallgren

and not at all to vitamin B_{12} The other members of the series respond variously and unpredictably to vitamin B_1 and more or less adequately to folic acid Subacute combined degeneration of the cord responds only to vitamin B_1 It is also possible to classify the megaloblastic anaemias according as the deficiency is primary as in nutritional macrocytic anaemia or conditioned as in pernicious anaemia where the most important factor appears to be the atrophy of the secretory cells of the stomach

In most of the dyshaemopoietic anaemias lesions occur in the mouth the pharynx and the stomach The oral and pharyngeal lesions are secondary and clear up when the anaemia is effectively treated The gastric lesions may be primary or secondary In pernicious anaemia the gastric atrophy appears to be primary and is unaffected by treatment whereas in sprue gastric secretion is depressed during the active stage but may return to normal afterwards In chronic hypochromic anaemia achlorhydria and hypochlorhydria when present are not much affected by treatment of the anaemia nevertheless the possibility remains that long standing iron deficiency has irreversibly damaged the gastric mucosa Descriptions of well preserved material from the alimentary tract of patients with dyshaemopoietic anaemia are relatively few and sometimes contradictory Some of the lesions originally reported were the result of post mortem degeneration which must be avoided by examination during life or by fixing the tissues immediately after death

TABLE I

DIFFERENT POSSIBLE CAUSES OF DECREASED REGENERATION OF LINGUAL PAPILLAE

Enzyme	Prosthetic group	Disease	Therapy
1 Deficiency of redox enzymes			
Warburg s iron porphyrin enzyme	Porphyrin + Fe-	Sideropenia	Iron
Cytochrome	Porphyrin + Fe-	Sideropenia	Iron
Flavine enzyme	Riboflavine	Ariboflavinosis	Riboflavine
Pyridine enzyme	Nicotinic acid amide	Pellagra	Nicotinic acid
2 Deficiency of anti pernicious anaemia factors probably necessary for cell division			
—	Vitamin B_{12}	Pernicious anaemia	Vitamin B_{12}
—	Pteroyl glutamic acid	Nutritional macrocytic anaemia sprue etc	Folic acid
3 Increased metabolism			
—	—	Streptococcal septicaemia hyperthyroidism	—

The changes which occur in the mouth pharynx and stomach in chronic hypochromic anaemia and pernicious anaemia are angular stomatitis glossitis the Plummer Vinson syndrome and achlorhydria Similar changes are observed in ariboflavinosis pellagra and Sjögren s syndrome The reason why the same end result may occur in different diseases is that the epithelium of the upper alimentary

dysphagia (Bicknell and Prescott 1946) In ariboflavinosis there may be not only angular stomatitis but also cheilosis that is redness scaliness and crusting of the vermilion of the lips The colour of the tongue is described as purple or magenta the filiform papillae lose their keratin tops and become mushroomed out and later patchy denudation may occur leading to a geographical tongue Inflammatory lesions also occur about the nostrils the palpebral fissures the vulva prepuce scrotum and anus Similar manifestations are unusual though not unknown in the iron and liver deficiency anaemias Corneal vascularization and optic atrophy are late but pathognomonic signs of ariboflavinosis (Stannus 1944)



FIG 3 —Glossitis of an aphthous type in a woman with achlorhydria and hypochromic anaemia the glossitis was resistant to treatment

Sjögren s syndrome or kerato conjunctivitis sicca is characterized by dry eyes a dry mouth and swollen parotid glands These changes are due to inflammation and atrophy of the lacrimal and salivary glands and fissures may develop on the tongue and lips Sjögren s syndrome is frequently associated with evidences of chronic systemic infection such as arthritis anaemia and increased sedimentation rate It is probably a variant of rheumatoid arthritis and any anaemia or iron deficiency which may be present is symptomatic and not causal (Stenstam 1947) Aphthous ulcers of the mouth (Fig 3) occasionally occur in chronic hypochromic anaemia and pernicious anaemia but there is probably no causal connection In recurrent aphthous ulceration of the mouth there may be coincident ulceration

(1923) found that pathological changes are always present in the tongue after death in untreated cases of pernicious anaemia even though they were not visible in life A striking departure from the normal consists in the weak development of the filiform and fungiform papillae The points of the filiform papillae are rounded off and the primary papillae in the connective tissue are reduced to low flat hill shaped formations Wallgren found the muscle of the tongue normal in con trast to Hunter (1909) and Schneider and Carey (1927) *who reported not only* atrophy of the mucosa and submucosa but also a lessened muscle volume Wallgren also disagreed with these observers in finding that bacteria were rarely present in the tissues only once in 13 cases

Something like half of the number of the patients with pernicious *anaemia* coming under treatment at the present time complain of soreness of the tongue In some there is a burning sensation alone without visible change Later the tongue becomes red and inflamed with superficial ulceration This inflammation may involve only the tip and edges of the tongue or the entire buccal cavity Symptoms may remit for a time but successive attacks lead to denudation of the papillae of the tongue which eventually becomes smooth glossy and shiny Even when completely bald it is liable to attacks of inflammation with patches of angry redness Soreness and inflammation are rapidly relieved by treatment with liver or vitamin B_1 and in the majority of cases the filiform papillae regenerate to a greater or lesser degree

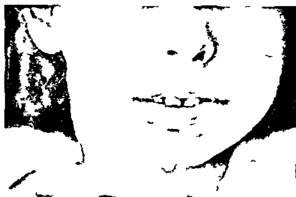


FIG 2 —Agranulocytic infection with perforation of lower lip in idio pathic steatorrhoea in a female aged 14 years recovery with trans fusion and intramuscular injection of liver extract (case of Dr A M Cooke) Agranulocytosis is not very uncommon in steatorrhoea though it rarely if ever occurs in pernicious anaemia

Glossitis occurred in 44 per cent of Lundholm s (1939) cases of idiopathic hypochromic anaemia being more frequent when the anaemia was severe A blotchy irregular denudation of the papillae with absence of the epithelial tufts of the filiform papillae and often dusky irregular spots is said to be characteristic It is doubtful however whether the sore tongue of iron deficiency can be distin guished clinically from that of liver deficiency at any rate nowadays when effective treatment is given early Identical changes in the tongue may also be seen in sprue nutritional macrocytic anaemia and pernicious anaemia of pregnancy (Wills 1948)

In pellagra the tongue is more scarlet and swollen giving a beefy appearance It is more indented by the teeth there is a special tendency to aphthous ulceration and there is a generalized angry stomatitis which may spread downwards causing

dysphagia (Bicknell and Prescott 1946) In ariboflavinosis there may be not only angular stomatitis but also cheilosis that is redness scaliness and crusting of the vermilion of the lips The colour of the tongue is described as purple or magenta the filiform papillae lose their keratin tops and become mushroomed out and later patchy denudation may occur leading to a geographical tongue Inflammatory lesions also occur about the nostrils the palpebral fissures the vulva prepuce scrotum and anus Similar manifestations are unusual though not unknown in the iron and liver deficiency anaemias Corneal vascularization and optic atrophy are late but pathognomonic signs of ariboflavinosis (Stannus 1944)



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in the vulva vagina and anus and inflammatory lesions in the eyes the triple complex of Behcet The lesions are probably infectious or allergic in nature and though dysphagia and anaemia may develop with a superficial resemblance to the Plummer Vinson syndrome the lesions do not respond to haematinic remedies

Dysphagia and anaemia

The Plummer Vinson syndrome better known as the syndrome of anaemia glossitis and dysphagia was probably first reported by Paterson in 1906 (Paterson 1937) It occurred in 19 per cent of Lundholm s series of chronic hypochromic anaemia *It is rarely diagnosed in association with pernicious anaemia though* Wallgren (1923) found degenerative changes in the epithelium of the oesophagus in all of a series of 12 untreated cases of pernicious anaemia It is almost always associated with angular stomatitis and the patient has usually had all her teeth extracted The reason why dysphagia is rare in pernicious anaemia is probably that patients with untreated pernicious anaemia do not live long enough to develop this symptom Women with dysphagia and anaemia tend to be older than the average woman with chronic hypochromic anaemia the anaemia is more severe and the spleen is more often enlarged

These findings suggest that a long period of deficiency must occur before the patient develops dysphagia and this is in keeping with the apparent diminution in the number of cases in recent years The older theory that a hysterical dysphagia caused nutritional deficiency and anaemia has been finally abandoned though it is probable that the dysphagia aggravates the anaemia and that may be the reason why the symptoms persist after the menopause Milder degrees of dysphagia can often be elicited on questioning patients with typical idiopathic hypochromic anaemia and there is no sharp dividing line It is true that dysphagia may be the first symptom of which the patient complains but it has been shown that anaemia may precede the dysphagia the dysphagia is relieved by treatment of the anaemia and the anaemia may relapse without recurrence of the dysphagia (Witts 1931)

The food sticks at the upper end of the oesophagus and the patient localizes the discomfort at the level of the larynx Only liquids or soft food can be taken and the business of eating is often so slowed down that a meal comes to need an hour *With more rapid eating the food and liquid tend to dam back* overflowing into the trachea with paroxysms of choking and strangulation The patient is unable to take meals in public and prefers to eat with a bowl in front of her On inspection the mucosa of the tongue is glossy and sometimes shows leukoplakia as does the buccal mucosa The mucosa of the pharynx is dry often atrophic and the pharyngeal reflexes are depressed The hypopharynx may show superficial ulceration and leukoplakia There is a stricture at the mouth of the oesophagus usually due to spasm which can be overcome by the pressure of a bougie The entrance may however appear as a pinhole or irregular slit or it may be closed by a thin mucous web or tense band which is easily ruptured by the passage of the endoscope (Gerlings 1940) After the passage of the instrument erosions or fissuring may be seen at the mouth of the oesophagus Webs are easily overlooked as they are *readily broken down leaving only a faint tear but in other cases they may be seen as* a transparent veil sweeping across the anterior part of the oesophagus in the postcricoid area (Mervyn Thomas 1947) The formation and structure of the webs

is debatable but as they are so tenuous and can disappear on iron therapy alone it is believed that they are made up of thin films of desquamating tissue

The appearances on radiography (Fig 4) have been described by Waldenström and Kjellberg (1939) Gerlings (1940) and others It is essential to use a thick barium swallow and to have a series of films in various phases of deglutition Frontal and sagittal views should be taken with short exposures of approximately 0 03 seconds

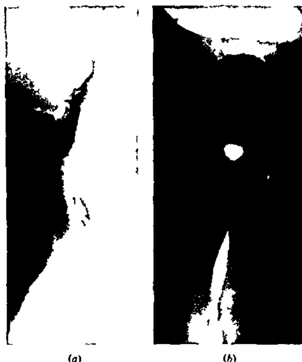


Fig 4 —Female aged 51 years with Plummer Vinson syndrome of dysphagia and anaemia defective clearance of pharynx and diaphragm stricture of hypopharynx (*a*) Lateral (*b*) antero-posterior skiagram

(*a*) (*b*)

The site of the lesion is usually the upper part of the oesophagus below the cricoid cartilage and changes are most clearly or even exclusively seen in the lateral view The most characteristic finding is one or more filling defects pointing from the anterior wall into the lumen at about a right angle They correspond with the picture seen on oesophagoscopy of a thin semilunar membrane on the anterior wall stretching towards the lateral walls of the gullet Filling defects may be seen only on maximal dilatation of the oesophagus In more advanced cases they are visible in the frontal view with indentation of the lateral wall there may be a circular fold or even a cuff like stricture of the oesophageal wall sometimes with a bulb like swelling of the hypopharynx above There may be stagnation of the meal in the valleculae and the pyriform fossae

A number of autopsy reports are available but some of the cases were atypical (McGee and Goodwin 1938 Savilahti 1946) Suzman (1933) has described the findings in a classical case The tongue showed much keratinization of the epithelium with desquamation and thinning in some areas there was considerable diminution

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In chronic hypochromic anaemia achlorhydria is inconstant though more frequent than normal In Lundholm s large and representative sample of cases 67 per cent of the patients had achlorhydria in the Ewald test meal and of these again 64 per cent secreted no free hydrochloric acid after histamine In some of the patients studied by Hartfall and Witts (1933) the juice was indistinguishable by ordinary tests from that in pernicious anaemia being deficient in volume pepsin and chlorides as well as in acid It was concluded however that intrinsic factor was present though only a small amount might be demonstrated Castle Townsend and Heath (1930) had previously reported the presence of intrinsic factor in patients with hypochromic anaemia and achlorhydria

It is generally agreed that in pernicious anaemia the gastric lesion precedes the development of anaemia The cause of the atrophy of the secreting cells is not known except for the negative information that it is not usually the result of an inflammatory gastritis All that is certain is that in some families there is a hereditary tendency to pernicious anaemia and that the incidence of the disease rises progressively in each decade Pernicious anaemia is a disease of people of European descent whose staple cereal is wheat It is rare in Asiatic and negro peoples though it is known to occur in negroes living in the United States of America Within the populations affected it shows no special social incidence Achlorhydria on the other hand is commoner in subtropical and tropical climates than in temperate zones *and in Europe it is more frequent in the less well nourished* sections of the population The specific nature of the alimentary lesion in pernicious anaemia still seems to elude definition

The relation of achlorhydria to iron deficiency is likewise ambiguous Iron deficiency may have at least three causes—defective diet defective assimilation and increased demand for haemoglobin—but the increased demand in females for haemoglobin for the reproductive function is the most important cause Iron is absorbed in the ferrous state which is favoured by the presence of free acid in the stomach Nevertheless this is only one of the factors affecting the absorption of iron The presence of reducing substances such as ascorbic acid and the products of protein breakdown and the amount of calcium and phosphorus in the diet are at least as important Achlorhydria decreases the retention of iron from a normal diet (Barer and Fowler 1936) but it is doubtful whether the acid is of paramount importance and there is no correlation between haemoglobin values and gastric acidity in the population in general (Brummer 1950) In diseased states people with a low haemoglobin tend to have a low acidity and here it is probable that the low haemoglobin is depressing the gastric secretion (Alvarez and Vanzant 1936) Hypochromic anaemia quite commonly develops after operations on the stomach which neutralize or abolish the gastric secretion but the disturbance in intestinal functions consequent on such operations is probably more important than the absence of free acid

In rare cases of iron deficiency anaemia there is evidence of a hereditary tendency to achlorhydria associated with pernicious anaemia in other members of the family (Heath 1933) Apart from such families and from cases associated with steatorrhoea it is unusual for achlorhydria associated with iron deficiency to terminate in pernicious anaemia Achlorhydria has sometimes been demonstrated

in the musculature The epithelium of the oesophagus was affected throughout with extensive desquamation of the hyperkeratinized epithelium The submucosa showed a moderate degree of infiltration with mononuclear cells Both the striated muscle of the proximal portion and the smooth muscle of the remainder of the oesophagus showed degenerative changes The intermuscular nerve plexus of Auerbach was normal

Differentiation from malignant disease is important and it may be difficult in patients with a cuff stricture Carcinoma of the hypopharynx occurs characteristically in middle aged and elderly females and it is believed that many of the cases supervene on the *Plummer Vinson syndrome (Ahlbom 1936) In uncomplicated* cases of dysphagia and anaemia administration of iron usually relieves all the symptoms The passage of a bougie may help but it should be done with caution owing to the risk of perforation Clinical improvement may occur without change in the skiagram

The stomach in the iron and liver deficiency anaemias

The pathological anatomy and physiology of the stomach in the dyshaemopoietic anaemias are not yet completely explored and a brief account must therefore be rather dogmatic Achlorhydria should be regarded as essential to the diagnosis of Addisonian pernicious anaemia Cases diagnosed as pernicious anaemia with normal gastric secretion can always be better classified under one of the other headings of megaloblastic degeneration of the bone marrow The most common cause of error is an undetected steatorrhoea The achlorhydria of pernicious anaemia is also final and irreversible Exceptions to this rule, which were more commonly reported in the older literature than today are usually the result of errors in diagnosis or classification

The reduction of gastric secretion in pernicious anaemia appears to be more complete than in any other disease It affects not only the hydrochloric acid pepsin and rennin but also the ferment like component described by Castle (1929) as intrinsic factor Intrinsic factor has not been isolated but in man it appears to be derived from the body of the stomach (Fox and Castle 1942 Landboe Christensen and Plum 1948) Agren has endeavoured to show that intrinsic factor *is identical with a ferment amino polypeptidase which can be isolated from the* pyloric mucosa of the hog but his experiments like most others in which concentrates of gastric juice and mucosa have been used are clouded by the possibility that the concentrates are themselves active owing to the presence of vitamin B_1 (Agren and Waldenstrom 1947) The main action of intrinsic factor appears to be to combine with vitamin B_1 and facilitate its absorption If the gastric secretion of intrinsic factor is the crucial fault in pernicious anaemia it is difficult to explain why a number of people who have lived for many years after total resection of the stomach and have not received specific anti anaemic therapy have nevertheless escaped pernicious anaemia (McDonald and others 1947) It is difficult to avoid the conclusion that some intrinsic factor may be secreted in the small intestine and there is some evidence for this in animals (Byron Hall 1950) though none in man *(Paulson and others 1950) Large amounts of vitamin B_1 are produced by the* bacteria in the large intestine in health and in pernicious anaemia but it is apparently not absorbed from there

non inflammatory atrophy in a series of 62 unselected post mortem examinations though he found that inflammatory gastritis increased with age In spite of claims made by gastroscopists no morbid anatomical evidence has been found of regeneration of the gastric mucosa with successful treatment of pernicious anaemia (Doig and Wood 1950)

Jacobson (1939) has indicated that the anti anaemic activity of desiccated preparations of the alimentary tract of the pig as determined by Wilkinson (1940) and others corresponds very closely with the distribution of the argentaffin cells These are cells containing granules which stain black with silver solution and also have the unusual property of fluorescence in ultra violet light He claimed that argentaffin cells were either completely or almost completely absent from the stomach and intestine in pernicious anaemia and sprue He found that these cells occur normally in man in the cardia and pylorus but they are practically absent from the body of the stomach They are numerous in the duodenum and quite frequent in other parts of the small intestine Jacobson equated this distribution with that of intrinsic factor as found by Meulengracht in the pig but it is now known that in the human stomach the body is the most active fraction in the treatment of pernicious anaemia Jacobson thought that the cells contained a pterin a suggestion of great interest in view of the subsequent discovery of folic acid (pteroyl glutamic acid) but Gomori (1948) has concluded that argentaffin cells contain a resorcinol and has denied that they contain a pterin

Jacobson s views on the disappearance of argentaffin cells in pernicious anaemia do not appear to have been confirmed Magnus (1940) pointed out that owing to the replacement of large areas of gastric mucosa by typical intestinal epithelium more argentaffin cells were seen in the fundus in some cases of pernicious anaemia than in any other condition and Doig and Wood (1950) have commented on the large number of argentaffin cells in the stomach in pernicious anaemia This naturally does not dispose of the contention that the argentaffin cells are diminished in the intestine though such a disparity in behaviour would be anomalous More over Gillman (1942) was unable to demonstrate argentaffin cells in the stomachs of normal Bantu natives among whom pernicious anaemia has never been observed

Only scattered information is available about the morbid anatomy of the stomach in other dyshaemopoietic anaemias Faber (1935) in a typical case of idiopathic hypochromic anaemia found a diffuse follicular gastritis Wood (1950) reports that the lesion seen in hypochromic anaemia with achlorhydria is a chronic gastritis there is usually considerable atrophy but also much evidence of inflammatory change with polymorphonuclear cells goblet cells are much less commonly seen than in pernicious anaemia No abnormality was found in the gastro intestinal tract in sprue (Faber 1904 Mackie and Fairley 1934 Hanes 1942) or in coeliac disease (Thaysen 1932) Suarez and others (1947) reported post mortem findings in 16 cases of sprue in Puerto Rico The gastric mucosa was moderately atrophied in half the cases while there was chronic gastritis in all but 3 Distinct shortening and blunting of the villi of the small intestine were noted in half the cases accompanied by an increase in the number of plasma cells in the tunica propria There is no evidence that formalin was injected immediately after death in Suarez s cases and results are misleading if this is not done Wallgren (1925) found no abnormality in the stomach and intestines in two cases of Addisonian anaemia associated with

before the development of iron deficiency anaemia and it is usually little affected by the treatment of the anaemia

Against this evidence for the priority of achlorhydria in iron deficiency anaemia it has been argued that the mucous membrane of the stomach is sensitive to nutritional deficiencies as is shown by the race and class incidence of achlorhydria and by the occurrence of achlorhydria in avitaminosis B_1 and B_2 It is therefore possible that achlorhydria in hypochromic anaemia is more often the result of iron deficiency than the cause (Davidson and Fullerton 1938) If it is a secondary phenomenon like glossitis and koilonychia it is unlike them in being usually irreversible Once achlorhydria is established a vicious circle will be present and the weight of the evidence suggests that this circle more commonly begins with iron deficiency than with achlorhydria Some support for the view that achlorhydria is the result of long standing iron deficiency is given by the age incidence Chlorosis which was an iron deficiency anaemia occurred in girls in their teens *the most frequent ages in Campbell s (1923) series being 16 17 and 18 years* The acidity of the gastric contents was high in 58 per cent normal in 14 per cent and low in 28 per cent A small series of cases of hypochromic anaemia treated at Oxford in the last decade had been analysed with special care to exclude bias in selection gross bleeding steatorrhoea or other complications The incidence of achlorhydria rose steadily with age

Age	*No o cases*	*Achlor hydria*	*Per centage*
15–24	7	1	14
25–34	15	6	40
35–44	25	12	48
45–54	19	13	68

Morbid anatomy of stomach in anaemia

Pioneer work on properly fixed specimens of the stomach in pernicious anaemia was carried out by Scandinavian workers who found a pronounced gastritis with or without severe atrophy of the mucous membrane (Wallgren 1923 Faber 1935) Meulengracht (1939) emphasized that the pylorus and duodenum were to all intents normal Magnus (1946) divided simple gastritis into inflammatory and non inflammatory types The inflammatory type leads to atrophy of the glandular parenchyma fibrosis of the mucosa and submucosa and intense infiltration of the interstitial tissue by plasma cells and lymphocytes It may be diffuse or it may be confined to the pyloric antrum Non inflammatory gastritis is confined to the body area of the stomach involving the whole thickness of its wall but not affecting the pyloro duodenal region Magnus and Ungley (1938) concluded both from their own specimens and from the Scandinavian descriptions that non inflammatory *gastritis* was the lesion found in pernicious anaemia

Magnus s description of the stomach in pernicious anaemia (*see* Chapter 14) has been confirmed by subsequent authors (Cox 1943 Wood and others 1949) It is coming to be agreed that non inflammatory atrophy usually associated with considerable intestinal metaplasia is the pathognomonic lesion in the stomach in pernicious anaemia Wynn Williams (1950) found no example of diffuse

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The essential factor in macrocytic anaemia of intestinal origin appears to be stagnation whether from intestinal stenosis or in the stagnant loop The syndrome differs from Addisonian pernicious anaemia in that the secretion of hydrochloric acid and intrinsic factor may be normal and from sprue in that there need not be steatorrhoea The stagnation brings about a change in the bacterial flora of the small intestine which may interfere with the absorption of folic acid and vitamin B_{12} or lead to the formation of toxic or haemolytic substances

Anaemia after gastric operations

At this point something should be said about the effect of operations on the stomach on blood formation A total gastrectomy deletes the whole of the secretion of acid and an unknown fraction of the intrinsic factor In health both the hydrochloric acid and the period of delay in the stomach help the solution of the iron in the food and its reduction to the ferrous state in which it is absorbed In experimental animals and probably in man too defective absorption of iron is one of the invariable consequences of loss of the stomach (Balfour and others 1950) After total gastrectomy the jejunal segment of the anastomosis dilates to form a reservoir probably at some cost to its absorptive efficiency Fat excretion is increased usually slightly but sometimes considerably and radiological examinations reveal a deficiency pattern in the small intestine Nitrogen excretion shows less variation from the normal (MacDonald and others 1947) Similar but less gross changes occur after partial gastrectomy and gastro-enterostomy (Wollaeger and others 1946) After the last two operations at any rate it is probable that interference with intestinal absorption is more important than interference with the gastric secretion in predisposing to anaemia

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prophylactic use of iron and liver Pernicious anaemia has occurred after both partial gastrectomy and gastro-enterostomy but the numbers are small in relation to the number of operations (Smith 1941) Hypochromic anaemia on the other hand is undoubtedly common particularly in women In a small series of patients examined 1-2½ years after a Polya gastrectomy at Oxford 1 in 3 of the men and 3 in 5 of the women were below the normal range of haemoglobin for their sex (Ward MacQuaid 1949) Larger series have recently been reviewed by Watson (1947) and Lyngar (1950) Operative treatment of gastric disorders is at present in a dilemma where removal of too little stomach is followed by recurrences and removal of too much by deficiency syndromes In anaemia after gastric operations a low residue low fat high protein high vitamin diet such as would be used for sprue is usually desirable Iron is often better tolerated and more effective when given intravenously In the rare megaloblastic type of anaemia folic acid by mouth may be more effective than liver or vitamin B_{12} by injection but it should be supplemented by liver or vitamin B_{12} owing to the risk of subacute combined degeneration

LEUKAEMIA HODGKIN S DISEASE AND ALLIED DISORDERS

Leukaemic manifestations in the alimentary tract have been reviewed by Forkner (1938) Leukaemias are divided into acute and chronic forms The acute leukaemias are subdivided into myelocytic lymphocytic and monocytic forms the chronic into myelocytic and lymphocytic According to the degree to which the blood stream is invaded by the abnormal cells the leukaemias may be further described as leukaemic leukopenic or aleukaemic Leukopenic variants are particularly common in acute leukaemia and in chronic lymphocytic leukaemia in both of which there may be gross infiltration of the alimentary tract in the presence of only small changes in the total and differential white cell count Chloroma and multiple myeloma are classes of leukaemia which are characterized by local tumours in bone and elsewhere but which rarely involve the alimentary tract directly Multiple myeloma should however be suspected in diffuse systematized amyloidosis which has a special tendency to involve the tongue as well as the muscles and joints in this form of amyloidosis macroglossia is often the presenting symptom whereas gastro intestinal symptoms are usually negligible (Lindsay and Knorp 1945) The pathognomic sign of multiple myeloma is the presence of myeloma cells in marrow puncture smears other features often present are abnormalities in the plasma proteins high erythrocyte sedimentation rate Bence Jones proteinuria and changes in the bones detected on clinical or radiological examination

Acute leukaemia

The constituent elements in the pathology of leukaemia are anaemia infiltration and a tendency to haemorrhage and necrotic ulceration In acute leukaemia haemorrhages may occur from any part of the alimentary tract A frequent manifes tation is haemorrhage from the gums often combined with necrotic ulceration of the gums and mouth and occasionally with Ludwig s angina Tumorous infiltration of the tonsils and the lymphoid tissue of the pharynx may also occur Similar

stomach should always raise the suspicion that some abnormal bleeding is occurring Even when no gross lesion can be demonstrated in a careful review the possibility of recurrent acute ulceration should remain in mind

MacDonald and others (1947) traced 46 patients who had lived for 3 years or more after total gastrectomy and who were not known to have received prophylactic treatment with liver In 12 the blood findings resembled those of pernicious anaemia and in 5 there was anaemia of a doubtful nature Ten of the remaining 29 patients who did not develop anaemia were known for certain not to have received prophylactic treatment Of the 12 patients who had anaemia of the pernicious type 6 had had non malignant lesions of the stomach and in the other 6 there was no sign of recurrence Gastrectomy had been successful and the diet was adequate Macrocytic anaemia seldom occurred less than 2 years after operation and 2 patients survived 10 and 20 years respectively without anaemia In idiopathic pernicious anaemia relapses occur any time from 2–38 months after ceasing therapy (Schwartz and Legere 1944) The cessation of substitution therapy in established pernicious anaemia thus produces a prompter and more constant effect on blood formation than the complete removal of the stomach

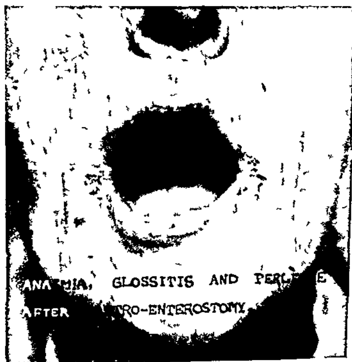


FIG 5—Angular stomatitis in a man who developed hypochromic anaemia and glossitis after gastro-enterostomy

No useful purpose would be served by trying to give figures for the frequency of anaemia after different types of partial gastrectomy and gastro enterostomy (Fig 5) Technical procedures vary greatly as does the after care of the patients and the

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haemorrhagic and infiltrative lesions in the stomach and intestine will give rise to haemorrhage perforation or a clinical picture resembling typhoid fever

In acute monocytic leukaemia the mouth is involved in a peculiar and recognizable way sometimes called pseudo scurvy The gums become greatly swollen and overhang the teeth which are loosened Haemorrhage ulceration and necrosis subsequently occur and a cellulitis may spread into the tissues of the face These lesions are based on a diffuse infiltration of the tissues with monocytes Infection about the mouth in leukaemia can usually be controlled by systemic treatment with penicillin and the grosser forms of these unpleasant complications have become less common since its introduction Dental treatment should be conservative owing to the risk of uncontrollable bleeding

Chronic leukaemia

A haemorrhagic tendency is common in chronic myeloid leukaemia and the first symptom may be haematemesis and melaena rectal haemorrhage or haemorrhage into the mesentery or behind the peritoneum In such cases the finding of a palpable spleen usually suggests the need for a blood count which reveals the diagnosis Infiltration to a degree sufficient to produce symptoms is almost unknown in chronic myeloid leukaemia It is on the other hand well known in chronic lymphatic leukaemia though still rare The most striking manifestation is enlargement of the stomach and thickening of the mucosa which is thrown up into huge folds like the convolutions of the brain Similar infiltration may occur in the small intestine and both stomach and intestine may be involved in this way Other manifestations are enlargement of the Peyer s patches hyperplasia of the lymphoid follicles in the large intestine and enlargement of the abdominal lymph glands Intussusception may occur The usual symptoms are diffuse abdominal pain not closely related to meals diarrhoea which is sometimes severe and intractable and loss of weight proceeding to extreme emaciation and asthenia Occult blood and an excess of fat may be present in the stools Radiographic appearances are not characteristic and the lymphocyte count in the blood may not be notably increased Diagnosis may therefore depend on marrow puncture biopsy of a lymph gland or hepatic puncture

Hodgkin s disease and allied conditions

The abdominal manifestations of Hodgkin s disease are similar to those of lymphatic leukaemia and indeed the strict pathological diagnosis whether leukaemia Hodgkin s disease or lymphosarcoma is usually a problem for the expert (Jackson and Parker 1947) It has been stated that in any series of cancer of the small bowel half will be lymphomatous tumours of one type or another Craver and Herrmann (1946) classify Hodgkin s disease of the alimentary tract into primary secondary and extrinsic forms The primary form of which about 150 cases had been reported up to 1940 is of most interest to the gastro enterologist It may involve any part of the gastro intestinal tract but most commonly the stomach The majority of the patients are in the fifth decade and when the stomach is involved the clinical story and the radiographic appearances are indistinguishable from those of carcinoma the correct diagnosis being made only on microscopic

examination In the small intestine the symptoms are those of a localized obstruction or ulceration sometimes with fever anaemia and leukopenia so that there may be a resemblance to typhoid fever The importance of primary gastro intestinal Hodgkin s disease is that it does not appear to affect the body as a whole as ordinary Hodgkin s disease probably does from its inception and if the lesion is completely removed with its associated lymphatic glands the prognosis is much better than in the average case of Hodgkin s disease or cancer of the stomach A number of patients have remained alive and free from disease for 6-8 years after operation

In classical cases of Hodgkin s disease the prognosis is much more gloomy Complaints referable to the gastro-intestinal tract occur in about 13 per cent usually in the late stage of the illness Symptoms may be nausea vomiting diarrhoea which may be blood stained intestinal obstruction and in patients with hepatomegaly jaundice and ascites These symptoms are most often produced by extrinsic pressure of the enlarged abdominal lymph nodes or actual invasive growth Rarely there are intrinsic nodular lesions of Hodgkin s disease in the wall of the stomach or intestine Treatment of the secondary gastro-intestinal lesions of Hodgkin s *disease can only be symptomatic and will usually be by means of radiotherapy or* chemotherapy Involvement of the small intestine in sarcoidosis has been observed in a few instances either as part of a widespread or systemic sarcoidosis or as an isolated lesion the relation of such isolated lesions to Krohn s regional ileitis is controversial (Watson and others 1945)

HAEMORRHAGIC DISEASES

The haemorrhagic diseases can be divided into the purpuras and the coagulation defects The purpuras can be subdivided into thrombocytopenic and non thrombocytopenic and these again into primary and secondary forms It would be tedious to enumerate them in detail and it must be obvious that in any haemorrhagic state there may be bleeding and ulceration in the gastro intestinal tract Haematemesis and melaena may be the presenting symptoms in essential thrombocytopenic purpura (purpura haemorrhagica) but not commonly

Henoch s purpura

More important for the gastro-enterologist is Henoch s purpura the name commonly applied to that form of anaphylactoid or capillary purpura in which the lesions are characteristically visceral It is a non thrombocytopenic purpura due to increased capillary permeability which is commonly initiated by an infection such as a streptococcal sore throat and which has pathological affinities to acute rheumatism and nephritis The purpura is typically distributed over the extensor surfaces of the upper and lower limbs and the buttocks but such a distribution should not necessarily be expected in adults or in protracted attacks Joint pains are rarely absent the spleen may be palpable and the urine may contain albumin red cells and casts A good review of the abdominal manifestations has been written by Seneque and Gosset (1932) About 70 per cent of the patients with abdominal manifestations are males The syndrome occurs at all ages the incidence reaching a peak in the teens and falling off abruptly after 30 years It is a serious condition with a mortality of nearly 18 per cent

The abdominal symptoms are due to purpuric lesions under the serous and mucous coats of the stomach and intestine and in the parietal peritoneum In one fatal case on which I made a post mortem examination about a foot of the lower ileum showed gross oedema inflammation and ulceration and had eventually perforated Another patient had a short circuit for what was regarded as acute Crohn s disease but when the time came to excise the affected loop of bowel it was found to have recovered Another observer writes as follows (Widgery *1930*)

The diagnosis of Henoch s purpura was considered doubtful on account of the patient s age and since it seemed clear there was an abdominal emergency I operated the same day Several pints of straw coloured fluid came away and some coils of distended small intestine appeared On exploration I found a thickened piece of small intestine it was deeply congested with numerous subperitoneal haemorrhages throughout a length of 2 feet The walls were greatly thickened by oedema and the gut felt like a piece of hose pipe The intestine was distended above and collapsed below this Since it was evident that

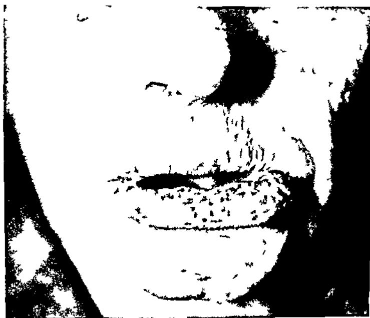


Fig 6—Hereditary haemorrhagic telangiectasia in a male aged 49 years This man presented with a severe hypochromic anaemia on inquiry there was a history of epistaxes and the stools contained occult blood (case of Dr E M Buzzard)

acute obstruction existed I performed a short circuit of ileum to ileum thinking the gut would recover Forty eight hours later an enema produced a satisfactory result One week afterwards a faecal fistula appeared only to close three or four days later Whether this was due to the breaking down of my anastomosis

or to gangrene of the loop I do not know The patient s recovery was uneventful except for three attacks of colic when solid food was first eaten but several more crops of petechiae with pyrexia appeared

The usual symptoms are abdominal pain of a colicky nature vomiting and melaena in rather less than 10 per cent of cases a tumour may be felt The abdominal symptoms precede the appearance of purpura in the skin in approximately a third of cases Senèque and Gosset classify their cases into typical cases without complications cases with peritoneal purpura simulating acute appendicitis and cases complicated by intussusception or perforation The differential diagnosis may offer great difficulty particularly in view of the fact that Henoch s purpura may be complicated by intussusception or perforation It is easy to say that when there is any doubt the abdomen should be explored but unfortunately the disease usually takes the form of a succession of outbreaks of purpura each perhaps with its own crisis of abdominal pain The duration of the illness is a matter of weeks or months and cases have been recorded lasting 2 and 4 years respectively Medical treatment is at present symptomatic but it is hoped that cortisone and adrenocorticotropic hormone will prove effective in aborting the illness

Haemophilia and multiple telangiectasia

Haemophilia is the most important condition in which there is defective coagulation of the blood Bleeding is usually but not exclusively the result of trauma Alimentary symptoms are rare and take the form of bleeding into the gastro-intestinal tract the peritoneal cavity or the abdominal parietes Treatment must be symptomatic transfusions being given freely to improve the clotting power of the blood and check the anaemia Although not a clotting defect hereditary haemorrhagic telangiectasia may be mentioned here inasmuch as it occurs with the same order of frequency as haemophilia and more often affects the alimentary tract giving rise to haematemesis melaena or fresh bleeding from the rectum The disease is inherited as a mendelian dominant and the diagnosis should therefore be suggested by the family history though sporadic cases occur Some telangiectases are I think invariably visible in the mouth on the lips (Fig 6) or on the skin Treatment is unsatisfactory owing to the multiple and recurrent nature of the telangiectases and operations to arrest and prevent bleeding from the alimentary tract can rarely hope to be successful

REFERENCES

Agren G and Waldenstrom J (1947) *Acta med scand Suppl* 196 432
Ahlbom H E (1936) *Brit med J* 2 331
Alvarez W C and Vanzant F R (1936) *Proc Mayo Clin* 11 385
Balfour D C Higgins G M and Woods K A (1950) *Ibid* 25 434
Barer A P and Fowler W M (1936) *Arch intern Med* 59 785
Bicknell F and Prescott F (1946) *The Vitamins in Medicine* 2nd ed London Heinemann
Brummer P (1950) *Acta med scand* 137 43
Byron Hall E (1950) *Brit med J* 2 585
Cameron D G Watson G M and Witts L J (1949) *Blood* 4 793 803
— — — (1950) *Brit J exp Path* 31 349
Campbell J M H (1923) *Guy s Hosp Rep* 73 247
Castle W B (1929) *Amer J med Sci* 178 748

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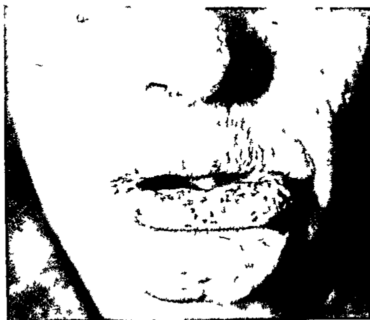


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REFERENCES

Watson G M (1950) *Proc R Soc Med* 64 957
Widgery F W (1930) *Brit med J* 2 243
Wilkinson J F (1940) *Ibid* 1 414
Williams A W (1950) *Ibid* 1 107
Wills L (1948) *Blood* 3 36
Witts L J (1931) *Guy's Hosp Rep* 81 193
Wollaeger E E Comfort M W Weir J F and Osterberg A E (1946) *Gastroenterology* 6 93
Wood J (1950) Personal communication
Wood I J Doig R K Motteram R Weiden S and Moore A (1949) *Gastroenterology* 12 949
Wynn Williams A (1950) *Brit med J* 1 107

Castle W B Townsend W C and Heath C W (1930) *Amer J med Sci* **180** 305
Cox A J (1943) *Amer J Path* **19** 491
Craver L F and Herrmann J B (1946) *Amer J Roentgenol* **55** 165
Davidson L S P and Fullerton H W (1938) *Edinb med J* **45** 1
Doig R K and Wood I J (1950) *Med J Aust* **2** 565
Faber K (1904) *Arch VerdauKr* **10** 333
— (1935) *Gastritis and its Consequences* London Oxford University Press
Forkner C E (1938) *Leukaemia and Allied Disorders* New York MacMillan
Fox H G and Castle W B (1942) *Amer J med Sci* **203** 18
Gerlings P G (1940) *J Laryngol* **55** 143
Gillman J (1942) *S Afr J med Sci* **7** 144
Ginsberg V and others (1950) *J Lab clin Med* **36** 238
Gomori G (1948) *Arch Path* **45** 48
Hanes F M (1942) *Amer J med Sci* **204** 436
Hartfall S J and Witts L J (1933) *Guy s Hosp Rep* **83** 3 24
Heath C W (1933) *Amer J med Sci* **185** 365
Hunter W (1909) *Severest Anaemias* Vol 1 London MacMillan
Jackson H and Parker F (1947) *Hodgkin s Disease and Allied Disorders* New York Oxford University Press
Jacobson W (1939) *J Path Bact* **49** 1
Jennings D (1949) *Lancet* **1** 547
— (1950) *Brit med J* **2** 575
Landboe Christensen E and Plum C M (1948) *Amer J med Sci* **215** 17
Lindsay S and Knorp W F (1945) *Arch Path* **39** 315
Lundholm I (1939) *Acta med scand Suppl* 102
Lyngar E (1950) *Ibid Suppl* 247
MacDonald R M Ingelfinger F J and Belding H W (1947) *New Engl J Med* **237** 887
McGee L and Goodwin T (1938) *Ann intern Med* **11** 1492
Mackie F P and Fairley N H (1934) *Trans R Soc trop Med Hyg* **27** 340
Magnus H A (1940) *Brit med J* **1** 415
— (1946) *J Path Bact* **58** 431
— and Ungley C C L (1938) *Lancet* **1** 420
Mervyn Thomas A (1947) *Amer J Roentgenol* **57** 213
Meulengracht E (1939) *Amer J med Sci* **197** 201
Mosbech J and Videbaek A (1950) *Brit med J* **2** 390
Patel J C and Bhende Y M (1947) *Indian med Ga* **82** 182
Paterson D R (1937) *J Laryngol* **52** 75
Paulson M Couley C L and Gladsden E S (1950) *Amer J med Sci* **220** 310
Savilahti M (1946) *Acta med scand* **125** 40
Schneider J P and Carey J B (1927) *Minn Med* **10** 215
Schwartz S O and Legere H (1944) *J Amer med Ass* **124** 637
Seneque J and Gosset J (1932) *J Chir Paris* **40** 828
Smith R (1941) *Middlesex Hosp J* **41** 114
Stannus H S (1944) *Brit med J* **2** 103 140
Stenstam T (1947) *Acta med scand* **127** 130
Suarez R M Spies T D and Suarez R M (1947) *Ann intern Med* **26** 643
Suzman M M (1933) *Arch intern Med* **51** 1
Thaysen T E H (1932) *Non tropical Sprue a Study in Idiopathic Steatorrhoea* London Oxford University Press
Waldenstrom J and Kjellberg S R (1939) *Acta radiol Stockh* **20** 618
— J (1941) *Uppsala Lak Foren Forh* **46** 215
Wallgren I (1923) *Uber die Veranderungen des Verdauungskanals bei der perniciosen Anamie* Jena Gustav Fisher
— (1925) *Arch a d Path Inst Helsingfors* **3** 275
Ward McQuaid N (1949) *Oxford Med School Ga* **1**
Watson A B (1947) *Brit J Surg* **34** 353
Watson C J Rigler L G Wangensteen O H and McCartley J S (1945) *Gastroenterology* **4** 30

REFERENCES

Watson G M (1950) *Proc R Soc Med* 64 957
Widgery F W (1930) *Brit med J* 2 249
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Wood J (1950) Personal communication
Wood I J Doig R K Motteram R Weiden S and Moore A (1949) *Gastroenterology* 12 949
Wynn Williams A (1950) *Brit med J* 1 102.

CHAPTER 2

THE RELATIONSHIP BETWEEN THE ALIMENTARY TRACT AND THE CARDIOVASCULAR SYSTEM IN DISEASE

K D KEELE

DISORDERS of the cardiovascular system and the alimentary tract may be related by 3 main mechanisms (1) By mechanical interference with function for example pressure from an aneurysm (2) by reflex disorders with or without production of pain and (3) by disorders of circulation such as congestion or ischaemia The relationship is often reciprocal particularly in the case of reflex disturbances These therefore commonly present problems in differential diagnosis

There may be also an aetiological relationship—both cardiac and gastro intestinal dysfunction may result from some primary disturbance of metabolic or endocrine nature as in von Gierke s disease or possibly in gall bladder disease Though the relationship between disease of both systems may be coincidental as in the aged gastro intestinal disease may precipitate cardiac symptoms as for example when an oesophageal diverticulum induces angina of effort Finally gastro intestinal disease may merely simulate cardiac disease presenting a diagnostic problem

HEART AND THORACIC AORTA IN RELATION TO *ALIMENTARY TRACT IN DISEASE*

The oesophagus and cardiovascular disease

By virtue of the close anatomical relationship of the heart and aorta to the oesophagus mutual mechanical and reflex interference is not uncommon and is becoming increasingly recognized by the aid of fluoroscopy and electrocardio graphy

Mechanical disturbance of the oesophagus producing dysphagia is remarkably uncommon considering the amount of distortion often produced by left auricular enlargement or aortic aneurysm Distortion also occurs in advanced atheroma of the descending aorta but dysphagia is rare Dysphagia does occur however with congenital abnormalities of the aortic arch and its branches

Dysphagia lusoria

This term was first used by Bayford in 1789 when describing a case of severe dysphagia in a woman who endured her distress until the age of 62 years at which time at autopsy she was found to have an aberrant right subclavian artery arising from a normal left aortic arch The term dysphagia lusoria derives from *lusus naturae* a jest or sport of Nature and its use to cover dysphagia due to this group of abnormalities of the aortic arch and its branches seems justifiable

The anomalies concerned are diverse but the commonest consist of (*a*) an anomalous subclavian artery arising from the left aortic arch whence it passes usually behind the oesophagus to emerge on the right side and (*b*) cases in which the ascending aorta passes to the right and instead of passing down the right side of the vertebral column is drawn to the left behind the oesophagus by a left sided ductus or left subclavian artery arising from a persistent left aortic root Both trachea and oesophagus are thus caught in a ring of vessels completed by the ductus arteriosus (*c*) The aortic arch is double a complete vascular ring being formed round trachea and oesophagus In such cases symptoms are produced not so much by displacement as by constriction of the trachea and oesophagus inside the abnormal vascular ring (*see* Fig 7)

The large majority of these anomalies produce no dysfunction When symptoms are produced they vary with age

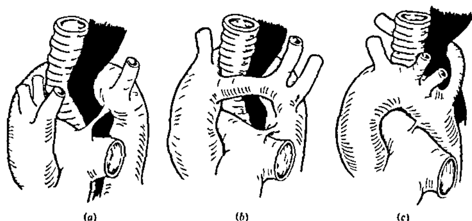


Fig 7 —(*a*) Left anterior oblique view of the deformity and constriction of the oesophagus and trachea produced by right sided aorta with persistent left aortic root (*b*) left anterior oblique view of the oesophagus and trachea in relation to a double aorta (*c*) left anterior oblique view of the oesophagus in relation to an anomalous right subclavian artery

In infancy and for the first few years of life respiratory disturbances produced by tracheal stenosis or by spill over from oesophageal obstruction predominate Stridor may be severe with rib recession on inspiration accentuated during feeding This simulates tracheal narrowing as with congenital laryngeal stridor or pressure by a mediastinal mass from without such as an enlarged thymus Dysphagia vomiting and feeding difficulties predispose to repeated respiratory infection

Later in life dysphagia and regurgitation come more prominently into the picture as in Bayford s case Diagnosis is made by following the course of a small barium swallow at fluoroscopy in the oblique positions About the level of the third thoracic vertebra the barium will be seen to make a curve convex anteriorly This appearance occurs with all the abnormalities described Further analysis of

the vascular anomaly may then be made by angiocardiography which will supply the surgeon with sufficient information to plan operation for relief of the constriction a feat first performed by Gross (1946) in cases of double aorta

The oesophagus and aneurysms of the thoracic aorta

Though aneurysms of the ascending aorta do not effect the oesophagus those of the arch and descending aorta may do so symptoms of dysphagia and regurgitation being produced in some cases earlier than the degree of mechanical obstruction would appear to warrant

Localized aneurysm formation of the transverse arch may induce dysphagia early but not without other signs of pressure on the recurrent laryngeal nerve or the left bronchus Fluoroscopy in such a case will show the oesophagus deviated to the right and posteriorly rather than anteriorly as with a congenital vascular ring Just above the diaphragm the oesophagus lies in front of the aorta and is closely attached to it thus with an enlarging aneurysm or with marked tortuosity of this part of the aorta the lower end of the oesophagus becomes grossly displaced usually *forwards and to the left An example of this is shown in Fig 8 In this case* of a woman of 80 years the presenting symptom was pain in the back there was no dysphagia The pain was attributed to the gross osteoarthritis of the spine present

Reflex relations of heart and oesophagus

Vago vagal effects—The innervation of the heart by the vagus and sympathetic nerve fibres from the first 4 or 5 thoracic segments of the spinal cord almost coincides with that of the oesophagus in the lower end of which the fifth and sixth thoracic segments are said to be most important with regard to pain sensation Reflex interaction between the two organs is close

Experimental work on animals has shown that the vagus has a vaso constrictor effect on the coronary arteries and that this reflex may be set up by distension particularly when applied to the region of the lower end of the oesophagus the cardia or the fundus of the stomach Such effects are inhibited by atropine or vagal section

Reflexes of the vago vagal type involve not only the sino auricular and auriculo ventricular nodes in the heart but the depressor mechanisms in the aortic arch and carotid sinus as well producing syncope The oesophagus is not a common site of origin of this reflex but it has been described by Weiss and Ferris (1934) and by Correll and Lindert (1949) in cases of oesophageal diverticulum In these swallowing induced heart block and syncope Electrocardiographically long periods of sino auricular block were seen as well as various degrees of auriculo ventricular block

The attacks were induced by the inflation of a balloon distending the oesophageal diverticulum and also by swallowing cold water particularly when cardiospasm was also present

Digitalis by its vagal action induced the syndrome in one case—without it none of the other stimuli was effective Atropine abolished these attacks

Such vago vagal reflexes have attracted more attention since vagotomy was

introduced in the management of peptic ulcer Electrocardiograms taken at operation reflect changes due to the anaesthetic as well as those resulting from vagal stimulation In some cases the anaesthetic has an effect analogous to that of digitalis described above and the vagal reflexes are potentiated in other instances they are diminished Prolongation of the P R interval sometimes occurs during dissection of the vagus



Fig 8 —Anterior convexity of the oesophagus with gross tortuosity of an atheromatous aorta (Case Ref 1613 49)

Pre-operative morphine and cyclopropane potentiate these effects whilst atropine barbiturates and ether diminish them Ether anaesthesia is considered the safest on account of its sympathomimetic action

It is apparent that the production of the syndrome depends on a pattern of factors in any individual case oesophageal spasm or diverticulum cold sino aortic sensitivity digitalis may all take part not one of them being justifiably termed the cause

Oesophageal and cardiac pain

Oesophageal pain is usually referred to the lower half of the sternum it may radiate up into the neck and into the left arm and back Such a distribution has raised the problem not only of differentiating between cardiac and oesophageal pain but whether indeed attacks of true angina pectoris are not produced by an

oesophageal rather than a cardiac mechanism Such an explanation is put forward to account for the results of experiments like those of Morrison and Swalm (1940) who produced angina by oesophageal dilatation with S T segment changes in the electrocardiogram similar to those seen in angina of effort Since such oesophageal dilatation causes coronary vaso constriction by vagal stimulation the mechanism of ischaemia of cardiac muscle may still have been operative Gilbert and others (1940) also have found that in patients breathing low oxygen mixtures anginal pain is produced more quickly after a meal than on an empty stomach an effect which can be abolished with atropine In this case too the anginal pain may be dependent on vagally stimulated vaso constriction of the coronary arteries which is released by atropine

Pain produced by myocardial infarction is not influenced by nitrites or atropine given in doses large enough to abolish all oesophageal spasm a fact strongly against the oesophagus being its site of origin

The relation of oesophageal to cardiac pain would appear to be (*a*) that similar areas of reference occur (*b*) that oesophageal stimulation may produce coronary vaso constriction in those with previous coronary disease or in old people with increased vagal tone and (*c*) that in the presence of cardiac ischaemia reflex spasm of the lower oesophagus takes place adding its component of pain In such cases both the cardiac and oesophageal sources of painful stimuli are abolished by trinitroglycerin As a result of the abolition of oesophageal spasm belching occurs coinciding with relief of pain

It is common to read reports of oesophageal pain being indistinguishable from angina It is not common to read what the criteria of indistinguishability were If in any individual case of substernal pain Ryle s ten questions are asked few instances of confusion with angina of effort arise Substernal pain may be related to effort in cases of cardiospasm but in such cases dysphagia and the sense of local obstruction retrosternally are present at rest apart from effort often with burning pain Effort may add the constricting sensation with dyspnoea relieved by rest In instances of such pain relief may be complete after cardioplasty

Other points in the distinction of oesophageal pain from angina of effort are its burning character radiation may occur down the left arm but very seldom down the right or both arms if felt in the back it is lower than the area of reference of cardiac pain and relief with alkalis is as usual with oesophageal as gastric pain but is not a feature of angina of effort

The resemblance to the pain of coronary occlusion is closer in that both appear at rest but oesophageal pain will be relieved by full doses of trinitroglycerin alkalis or atropine—the pain of coronary occlusion will not The burning character of oesophageal pain is not alone a reliable guide for there is no doubt that coronary occlusion may manifest itself sometimes as burning substernal pain—one of the ways of masquerading as indigestion

It is of course in the light of the full history and examination of the patient that the significance of substernal pain must be judged the associated phenomena of peripheral vascular failure usually being of first diagnostic importance with coronary occlusion Though electrocardiographic signs are often absent with angina of effort characteristic changes occur with cardiac infarction

Hiatus hernia in relation to coronary disease

In this condition both mechanical and reflex effects may simulate cardiac disease yet thoracic symptoms occur in only about 25 per cent

If the hernia is large displacement and rotation of the heart occurs with palpitation and dyspnoea possibly combined with left mammary discomfort However the large hernias are less often responsible for distressing symptoms than those which are small and tense Pain with these hernias is produced by three processes apart from mechanical displacement—by tension within the displaced sac oesophagitis and by stretching of the diaphragmatic ring These factors combine to produce pain in substernal left chest and left shoulder regions Substernal pain closely related to exertion is common in this condition So much so that Master Dack Stone and Grishman (1949) in an analysis of 57 cases came to the conclusion that the history was not a safe guide in the differentiation of cardiac disease from hiatus hernia The difficulty is accentuated by the frequency of blood loss in these cases producing anaemia with its own symptomatology In the abovementioned series the largest group consisted of cases in which cardiac disease and hiatus hernia were both present such patients had both gastro intestinal and cardiac complaints and in the presence of coronary disease hiatus hernia may precipitate coronary insufficiency

Spontaneous perforation of the oesophagus and myocardial infarction

This condition has become a diagnostic problem of first importance since its operability has been clearly established by Barrett (1946) Olsen and Clagett (1947) and Scholefield (1949) The differentiation from cardiac infarction and dissecting aneurysm of the aorta is the more difficult since it occurs mostly in middle aged males The rupture nearly always occurs just above the diaphragm the oesophageal contents passing into the mediastinum thence into the pleural sacs Symptoms are usually initiated by vomiting often after an alcoholic bout Dyspnoea cyanosis and shock with marked hypotension are usual Pain at first substernal or epigastric spreads rapidly to the back or to the left shoulder from diaphragmatic irritation Mediastinal emphysema may appear early over the upper chest spreading into the neck Pleural effusion appears on either side within a few hours Death occurs within 48 hours in untreated cases

In the differential diagnosis from cardiac infarction perforated gastric ulcer dissecting aneurysm and acute pancreatitis the early appearance of surgical emphysema and pleural effusion are most useful In the case of cardiac infarction a previous history of angina of effort with hypertension may be present Cardiac enlargement and the characteristic electrocardiographic signs will be present in about 90 per cent of cases if standard and a full set of precordial leads are taken Such changes however may take some hours to develop

Congestive heart failure and the intestinal tract

With congestive heart failure the gastro intestinal tract is affected by both diminution of blood flow and raised venous pressure Blood flow in the splanchnic circulation is found to be reduced approximately in proportion to the diminution in cardiac output Increased arteriovenous oxygen difference makes possible normal oxygen consumption in the early stages of failure

This proportionate diminution of blood flow is in contrast with the severe restriction of blood flow to the kidney in congestive heart failure

The *gastro intestinal tract as a whole does not show gross evidence of dysfunction* with these circulatory changes Food is digested and absorbed qualitatively normally though intake is diminished by anorexia and nausea Steatorrhoea and azotorrhoea do not occur Even the absorption of intestinal gas is not decreased and in spite of the presence of flatulent discomfort a normal amount of flatus is passed

Intestinal distension adds vagal reflex effects similar to those that arise from the oesophagus but less marked In addition mechanical elevation of the diaphragm by distension of the stomach or colon may interfere with cardiac action

The liver in congestive heart failure

The liver is the organ earliest involved by rise in venous pressure Increase in the tension of the capsule is the stimulus which produces pain In a patient with early right ventricular failure such distension is often transient on exertion thus *producing pain which is not unlike that of angina of effort This is especially so in* cases where the site of reference is to the epigastrium rather than to the right hypochondrium Such pain may occur with a liver that is not easily palpable since stretching of the capsule is more marked in early engorgement than later

Hepatic engorgement may occur before there is a general rise in venous pressure as reflected in the jugular or antecubital veins As congestive failure progresses the liver cells at the centre of each lobule atrophy and disappear whilst those farther out undergo fatty degeneration Though this nutmeg stage may go on to central lobular fibrosis it rarely advances to a periportal fibrosis sufficient to obstruct the portal circulation

According to Dock (1949) these changes are not accompanied by any reduction of liver metabolism and thus cellular anoxia is accentuated With grossly diminished cardiac output as in shock this factor may produce extensive hepatic damage not confined to the centre of the lobules

Though the severest degrees of impairment of liver function do not occur liver function tests may show impairment during congestive failure Urobilinogen in the urine is common The bromsulphalein test often shows retention This however may reflect failure of hepatic blood flow as well as hepato cellular damage The cephalin cholesterol flocculation test was 2 plus or more in 56 per cent of one series of cases of congestive failure but 30 per cent of normals were equally positive and it would appear that the reagent was unstable Collodial gold thymol turbidity and thymol flocculation tests are negative in first bouts of congestive failure but the thymol turbidity becomes positive in later bouts followed by the other two When this happens the prognosis according to Carter and Maclagan (1946) is poor Hyperbilirubinaemia is common and after a year of congestive failure practically constant but clinical cardiac jaundice develops in only about 5 per cent of cases Its presence depends on three factors (*a*) diminution of hepatic blood flow (*b*) impairment of liver function and (*c*) increase of bilirubin formation When the changes in the liver cells are limited to atrophy and fatty degeneration jaundice is of retention type—but if there is hepatocellular necrosis regurgitation takes place The presence of pulmonary infarcts or long standing pulmonary congestion increases bilirubin formation and favours the development of jaundice

Hepatic enlargement in congestive heart failure causes no diagnostic difficulty if it correlates with venous engorgement of the neck and dyspnoea But this correlation may be lacking or obscured by obesity and increased venomotor tone Direct measurement of venous pressure by manometer is sometimes necessary

At two phases of congestive failure however venous pressures may be normal (*a*) In the early stage whilst the liver is acting as a reservoir it may take up some hundreds of millilitres of blood before there is a rise of venous pressure (*b*) On recovery from congestive failure the liver again may hold a large quantity of blood after the venous pressure has dropped to normal

If there is hepatic enlargement and a rise in venous pressure with absence of dyspnoea obstruction of venous return as with constrictive pericarditis or triscuspid stenosis is suggested Enlargement of the liver with ascites without rise of venous pressure or dyspnoea is found with cirrhosis of the liver or thrombosis of the hepatic veins (Budd Chiari syndrome)

Congestive heart failure supervening in a patient with cirrhosis of the liver produces marked signs of pulmonary and venous congestion since the liver fails to act as a venous reservoir

The liver in constrictive pericarditis and hepatic vein thrombosis

These two conditions produce very similar effects on the liver This may be due in part to the high incidence of hepatic vein thrombosis which has been noted in cases of constrictive pericarditis

Histological changes in the liver are similar to those in congestive failure central lobular and periportal fibrosis are equally late in appearing The characteristic thickening of Glisson s capsule with constrictive pericarditis is probably due to the mechanical venous obstruction for it subsides slowly after this obstruction has been removed by successful pericardiolysis

Interesting confirmation of the importance of this mechanical factor has been made experimentally by McKee and others (1948) who obstructed the inferior vena cava to half its normal diameter within the pericardial sac in dogs This produced cirrhotic changes in the liver combined with an extensive formation of collateral circulation through adhesions formed between the omentum and the parieties as well as between the liver and the diaphragm Histologically the adhesions were found to be very vascular and there was marked hyperaemia of the subcapsular zone of the liver which contained grossly dilated lymphatics There was also enlargement of mediastinal and pleural vessels with an enlarged azygos vein

In relation to these findings it is of interest that Meyer (1947) in three cases of obliteration of the hepatic veins in children also found marked oedema of Glisson s capsule with dilated lymphatics It seems that the attempt to form a collateral circulation through the liver capsule and adhesions plays an important part in the formation of the thickening of the peritoneum so common in constrictive pericarditis

Thrombosis of the hepatic veins may originate from three main sites—in the veins themselves at their mouths or in the inferior vena cava This last site of origin of the thrombus occurs in about 50 per cent of cases Thompson (1947) lays emphasis on the importance of polycythaemia rubra vera and pregnancy in the aetiology

on epigastric pain and vomiting as initial symptoms passing on rapidly to hepatic enlargement with ascites and on the usual short duration of the acute form of the disease

The stomach and cardiac disease

When the stomach is distended by gas mechanical and reflex effects on cardiac action both operate After a meal the effect of a raised metabolic rate is added These factors acting on a healthy heart may produce extra systoles or paroxysmal tachycardia in a patient with diseased coronary arteries angina of effort may be precipitated

Substernal pain with gastric ulcer is not uncommon particularly in the presence of hypochlorhydria In such cases though the relation to food may be atypical pain is not related to exertion and is relieved by alkalis

When coronary disease and gastric ulcer are present it is remarkable how often the two pains are clearly differentiated by the patient However haemorrhage or perforation of a gastric ulcer may not only closely simulate coronary occlusion but on rare occasions may be followed by it during the period of shock I have also seen haemorrhage with shock precipitate congestive failure in hypertensive patients

The dietetic treatment of peptic ulcer involves a high calorie high fat diet and the consequent increase of weight is not favourable to cardiac patients It has been claimed that the incidence of coronary occlusion during treatment for peptic ulcer is unduly high and this has been attributed to the high fat diet with possible acceleration of atheromatous deposits in the coronary arteries Weight increase therefore in middle age or old age patients with peptic ulcer should be carefully controlled

With a large number of hypertensive patients having splanchnicectomy of recent years opportunity has arisen for noting the relationship of this operation to the occurrence of peptic ulcer There is apparently no increased incidence of ulcer symptoms in such patients but in those who had peptic ulcers previous to operation recurrence occurred in about 20 per cent Mason and Pollard (1949) found that in 11 out of 12 such recurrences haemorrhage or perforation took place in the absence of any previous typical pain This suggests that the occurrence of simple ulcer after splanchnicectomy is painless as expected and therefore that the true incidence of onset or recurrence of peptic ulcer following splanchnicectomy is not known only the complications being detected

The small intestine and cardiac disorders

The small intestine may influence cardiac action by (*a*) the mechanical factor in distension and displacement of the diaphragm (*b*) reflex vago vagal effects potentiating cardiac ischaemia with already diseased coronary arteries (*c*) by pressure on the inferior vena cava in such conditions as tuberculous ulceration with enlarged lymphatic glands and ascites In such cases venous pressure in the saphenous and femoral veins is raised whilst that in the arms remains normal Lastly (*d*) by defective absorption with disturbance of electrolyte and vitamin metabolism

The size of the heart is considerably influenced by fluid absorption In normal men ingestion of 1 litre of water has been shown to increase the transverse diameter by over 5 per cent and stroke volume by 35 per cent within 40 minutes (Casman 1947) It has been suggested that this fact may account for the size of so-called beer hearts In dehydrated states the heart is small Cases of sprue show this constantly in relapse but there is an increase in the transverse diameter as they emerge from this state with diarrhoea and loss of weight into the phase of remission and gain of weight although during this phase the loss of fat by steatorrhoea is unaltered For example in a personal case the increase of transverse diameter of the heart was from 10 3 to 12 8 centimetre in 1 month during which time a dramatic response to parenteral liver therapy was proceeding

How far such metabolic factors as plasma electrolytes and protein are responsible for the change in size is difficult to assess This also applies to observations on the electrocardiographic changes found in starved men during World War II

The effect of a meal on the normal electrocardiogram is an increase in rate the QRS complex increases in amplitude and there is left axis shift in the T wave The QT interval decreases proportionately to rate In starvation changes are in the opposite direction there tends to be reduction in amplitude of all waves with prolongation of the whole of electric systole affecting the PR QRS and QT intervals the last usually showing the most marked change In all cases these changes last 2-3 weeks after restoration of normal diet

Similar changes occur with thiamine deficiency but they are not thought to be specific In cases of pellagra the electrocardiographic changes are similar and it has been claimed that they may be corrected by niacin therapy (Rachmilewitz and Braun 1945) Thiamine therapy in these cases was ineffective However hypoproteinaemia neutralized the effect of niacin therapy

Of electrolyte changes inversion of the T wave in potassium deficiency is clear cut with its elevation on restoring the serum potassium level However an inversion of T wave due to left ventricular hypertrophy may also be similarly restored though not that due to myocardial infarction With alkalosis there is sometimes gross prolongation of the QT interval an effect possibly due to associated hypocalcaemia which it resembles

It will be noted that none of these metabolic derangements produces any gross ST deviation

The gall bladder and cardiac disorders

The association of cholecystitis and coronary disease raises the problem of aetiology as well as that of reflex relationship

It is often claimed that the coincidence of the two is so high that a common aetiology must exist Ryle found clinically recognized gall bladder disease in 9 per cent of 164 males with coronary disease and duodenal ulcer in 6 per cent He considers the incidence of duodenal ulcer to be no more than that of a random sample of the population but that of gall bladder disease higher From autopsy evidence Tennant and Zimmerman (1931) found arteriosclerotic heart disease in 126 of 694 consecutive autopsies on patients above 50 years old in 33 of these gall bladder disease was found that is in about 5 per cent When allowance is made for clinical recognition in Ryles cases an incidence of 9 per cent in males is suggestive

Kahn and Barsky (1928) too found gall bladder disease in 10 per cent of 200 cases of angina

Bockus (1946) however estimates that about 10 per cent of adults in the United States of America have cholelithiasis or are potential stone bearers Evidence thus still remains conflicting on this point the positive assertion of aetiological relationship is not established

Reflex relationship between the gall bladder and heart in relation to substernal pain is clearer In health both in dogs and human beings distension of the gall bladder produces no change in heart function nor pain resembling angina If dogs with lesions of the coronary arteries are used changes occur and in patients with coronary disease substernal pain may be precipitated with electrocardiographic changes Under these circumstances it is not surprising that following cholecystectomy in patients with coronary disease arrhythmia may cease and anginal attacks diminish in incidence

The nerve supply of the gall bladder (vagus and sixth thoracic to first lumbar segments of the sympathetic) does not overlap that of the heart Pain in gall bladder disease is usually confined to the right side and to dermatones supplied by the above segments—and so may become epigastric Spread to the segments of cardiac reference (thoracic first to fourth or fifth) is most probable when noxious stimuli are already reaching the cord from the heart in coronary disease Alternatively the vago vagal reflex producing coronary artery constriction may be brought into action and the pain be truly due to cardiac ischaemia Diagnosis in such cases depends on a complete clinical review of the case—and the incidence of disease of both heart and gall bladder in such cases with low substernal pain is considerable

Pain and tenderness in the right hypochondrium in early congestive heart failure with hepatic enlargement has been already mentioned Particularly in obese women this may simulate gall bladder disease

The "acute abdomen" and the heart

The difficulties of diagnosis in cases of severe abdominal pain with shock are due to (*a*) the common sensory reference of pain to the epigastrium from heart and abdominal viscera and (*b*) to reflex effects excited by one organ on another as well as the effects of low blood pressure in peripheral vascular failure which may dominate the picture

Previous history is of utmost importance in giving guidance as to the site of disease for example of angina of effort or of dyspepsia Quite often too the pain in the early stages shows a characteristic radiation as in a personal case of posterior coronary infarction with board like rigidity all over the abdomen and severe abdominal pain which had however radiated to the left elbow at the onset

Electrocardiograms may be altered in any of the abdominal catastrophes but do not show the gross ST deviation typical of anterior or posterior infarction though minor degrees of such deviation may occur from causes other than coronary occlusion Diagnostic difficulty is increased if *typical electrocardiographic changes* take hours or days to develop following cardiac infarction Dyspnoea may be a prominent symptom with coronary occlusion and oesophageal perforation The early development of pleurisy and surgical emphysema distinguishes the latter

Loeffler and Esselier (1946) stress the diagnostic importance of redness of the face and persistent hypertension during the acute phase of pancreatitis They also remark on the frequency of pericarditis and pleurisy with this condition Raised serum amylase or glycosuria may be of great diagnostic value here However hypertension may persist for many hours with coronary occlusion before the characteristic fall occurs and with dissecting aneurysm it often does not fall to low levels at all Blood pressure therefore cannot be taken as a very reliable diagnostic guide in the first few hours of acute abdominal pain

DISEASES OF THE ABDOMINAL AORTA AND SPLANCHNIC VESSELS

Diseases of the abdominal aorta produce diagnostic difficulty by three mechanisms —pain production the formation of an abdominal mass and vascular disorders in the bowel

Aneurysms—syphilitic or arteriosclerotic—may present with gastro intestinal symptoms such as abdominal pain vomiting haematemesis and weight loss simulating closely carcinoma of the stomach

As with arterial disease in general symptomatology is so variable that it is often difficult to analyse its mode of production Pain from pressure on neighbouring structures or the posterior abdominal wall may be of girdle type but slow though enormous increase in size may occur without pain Occlusion of branches of the aorta either temporarily by reflex or more permanently by atheroma or thrombosis would seem to be the commonest cause of symptoms Except in the rapid process of dissection of the wall little pain seems to be produced from disease in the aorta itself and in many cases the palpable tumour is not tender on pressure

Occlusion of the abdominal aorta

This condition first described as a pathological entity by Graham of Glasgow in 1814 was studied clinically by Gull (1857) in a case which survived 2 years after the event By 1899 Welch had collected 59 cases and since then it has become increasingly recognized The recent advent of aortotomy with removal of embolus for sudden occlusion and ligature or excision of the abdominal aorta as practised by the French raises its clinical importance

Pathogenesis

Pathologically complete occlusion of the abdominal aorta is always due to embolism or thrombosis with the very rare exception of coarctation of congenital origin

Embolism produces the dramatic picture of acute occlusion It occurs most commonly at the bifurcation of the aorta Following embolism thrombosis supervenes and may spread proximally and distally Proximal spread as it ascends occludes the branches of the aorta involving first the mouths of the lumbar arteries and the inferior mesenteric artery at which level it usually stops In some cases it spreads as high as the superior mesenteric and renal arteries Usually however the thrombus avoids the orifices of these arteries though spreading

past them Though the inferior mesenteric artery is the most commonly occluded there is usually a remarkable absence of infarction of the colon supplied by it Haemorrhagic infarction of the intestine was described in only 2 of 65 cases of aortic embolism collected by Hesse and quoted by Rothstein (1935)

Distal spread of thrombus may proceed down both common iliac arteries as far as the popliteal or posterior tibial arteries

Primary thrombosis may produce rapid or slow occlusion If rapid it may be impossible to decide conclusively whether the initial event was embolic or thrombotic This difficulty arises in cases of mitral stenosis for example the commonest group in which aortic occlusion occurs Slow thrombosis produces less dramatic symptoms as a rule both as regards the abdominal viscera and the legs, and it is *becoming increasingly common to find thrombotic occlusion of the aorta at* autopsy without symptoms referable to the event in life

Atheroma of the abdominal aorta is often gross—and it is not uncommon to find small formations of thrombus on atheromatous plaques partially occluding the lumen Such partial occlusion however produces no symptoms With a *slowly growing thrombus time is given for the development of collateral circulation* both in the lumbar and splanchnic vessels so that symptoms may be minimal This process accounts for the symptomless cases found at autopsy If for some reason collateral circulation does not develop symptoms are produced referred to the intestine or the legs

With occlusion of the abdominal aorta collateral circulation to the legs is maintained mainly through the lumbar arteries Experimentally the importance of this route was shown by Reichert and others (1934) in dogs Ligation of the aorta produced paralysis of the hind legs lasting only an hour Ligation of the lumbar arteries bilaterally produced similar transient paresis but ligation of both aortic and lumbar arteries produced complete paraplegia incontinence of urine and gangrene spreading up to the abdomen

Since the lumbar arteries supply the tip of the spinal cord, neurological effects may be produced by ischaemia in this region resulting in a spastic paraplegia with positive Babinski responses Such a condition occurring on walking was called intermittent claudication of the spinal cord by Dejerine

Aetiologically occlusion of the aorta is commonest in the presence of rheumatic heart disease mitral stenosis or coronary disease (both with auricular fibrillation) being present in about 80 per cent of cases Atheroma of the abdominal aorta is of course very common

Symptoms of aortic occlusion

With rapid aortic occlusion without the development of collateral circulation the full clinical picture results consisting of abdominal and paraplegic components Pain is usually sudden agonizing situated in the hypogastrium often radiating down both thighs or round to the back Within a few minutes paraplegia supervenes with coldness and numbness of both legs Shock is often marked

Examination of the abdomen is remarkable for the absence of rigidity and tenderness is not a feature There is absence of pulsation of the aorta and both femoral arteries however in a few proved instances femoral pulses have remained palpable

In such cases aortotomy with embolectomy will reverse the symptomatology I have seen a case with typical abdominal pain and bilateral paresis which showed marked improvement in 3 hours treated conservatively with papaverine and procaine infiltration with residual arterial occlusion in the left foot only in 3 days

With slowly progressive occlusion the clinical picture shows great variety Symptoms may be confined to the legs as for example intermittent claudication and cold feet as evidence of bilateral arterial occlusion Leriche (1940) has emphasized the infrequency of trophic disturbance in the legs in such cases and lays stress on impotence as a symptom This is due to failure of arterial supply to the corpora cavernosa so that erection cannot take place Slow extension of the thrombus may take place over years and produce little further symptomatology until superior or inferior mesenteric artery occlusion occurs

Inferior mesenteric artery occlusion

In the large majority of instances such occlusion produced no symptoms That infarction may take place is demonstrated by the following case

W B male aged 52 years (323? 47) Six weeks before admission this man experienced sudden onset of hypogastric pain colicky in nature Attacks of colic became more frequent and after 2 weeks diarrhoea commenced streaks of blood appeared in the stools There was some frequency of micturition One week before admission vomiting commenced

On admission he was pyrexial (temperature 99 4 pulse 108) Heart and lungs were normal Blood pressure 140 90 Abdomen showed no tenderness or rigidity Urine no protein no deposit Culture sterile Electrocardiogram was normal Proctoscopy showed prolapsed haemorrhoids Blood count Hb 72 per cent R B C's 3 600 000 W B C's 13 000 per cubic millimetre Polymorphs 88 per cent lymphocytes 9 per cent Bleeding time 1 minute Clotting time 45 seconds Platelets 800 000 per cubic millimetre Erythrocyte sedimentation rate 61 millimetres in one hour W R negative Stools on microscopy showed blood and mucus pus cells Culture repeatedly failed to isolate any pathogen Sigmoidoscopy showed appearances typical of ulcerative colitis Barium enema showed rapid flow of enema through the descending colon which showed almost complete loss of haustration The caecum and ascending colon looked more normal The appearance was that of ulcerative colitis (*see* Fig 9) Progress The patient was treated with sulphasuccidine and penicillin without effect He continued to pass 5-10 bloody stools per day Two weeks after admission he complained of cold feet and noted weakness of the legs Frequency of micturition increased and he gradually became incontinent of urine and faeces

Three weeks after admission examination showed both femoral pulses palpable Both feet and legs were cold and white to the level of the knees All forms of sensation touch pin prick pressure vibration and pressure pain were absent to the level of the knee on both sides Joint sense was absence at the ankles At the time of examination *there was no pain in the legs Both legs* showed a flaccid paresis involving ankle and knee joints Knee and ankle jerks were absent Babinski reflexes not obtainable During the next few days pain appeared in the left foot and thigh more than on the right The femoral pulses were palpated within 24 hours of death which occurred 3½ weeks after admission 9½ weeks after the onset

Post mortem examination—There was no evidence of gangrene of the extremities Heart small coronary arteries healthy slight atheroma of the thoracic aorta Lungs emphysematous All abdominal viscera were normal except for the large intestine

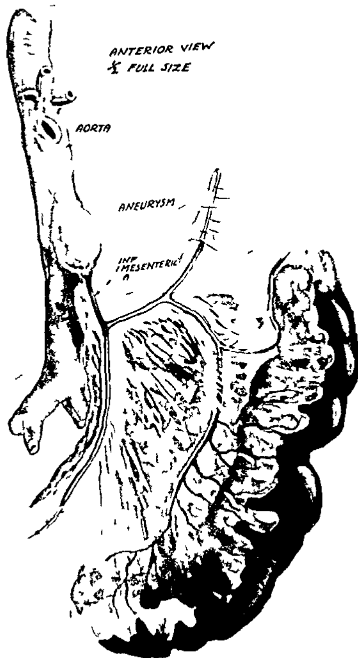


Fig 9—Aneurysm of the root of the inferior mesenteric artery with thrombosis and infarction of the colon s en from the front (Case Ref 3232/47)

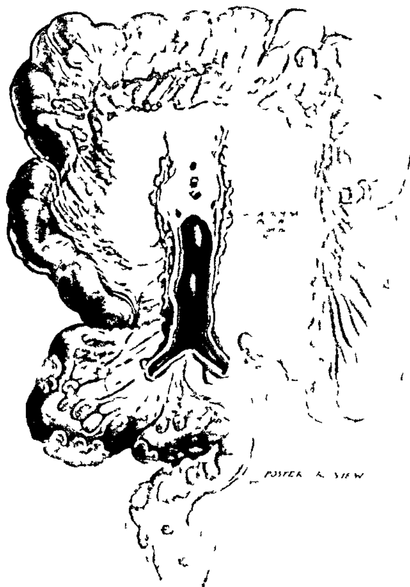


FIG 10—Thrombosis of the abdominal aorta with inferior mesenteric occlusion seen from behind in the same case as Fig 9 showing upward spread of the aortic thrombus and the area of colon involved by gangrene (Case Ref 3232/47)

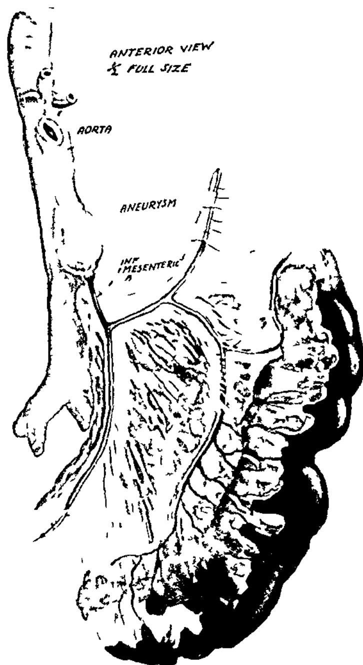


FIG 9—Aneurysm of the root of the inferior mesenteric artery with thrombosis and infarction of the colon seen from the front (Case Ref 3232/47)

was thought to be responsible for the haemorrhagic infarction of the colon noted by Campbell and Henderson (1949) in 3 cases of renal cortical necrosis.

This case also illustrates the absence of abdominal tenderness and rigidity during the early stages of intestinal ischaemia. This early stage may last only a few hours with gross and sudden occlusion, but it is not uncommon for subacute cases to have repeated attacks for days or weeks before intestinal infarction produces peritoneal irritation.

Superior mesenteric arterial occlusion

The difficulty of diagnosis until final gangrenous changes have taken place in the gut has directed interest in this condition towards the surgical emergency so produced.

In many cases which have come to operation there is a previous history of bouts of abdominal colic and vomiting suggestive of transient vascular occlusion, which in the absence of any satisfactory methods of investigation have not been traced to their true source.

As with other arteries there is great variability in symptoms, and complete occlusion which has produced few or no symptoms during its development is recognized, as in the following case.

H. H., female, aged 85 years (3979/48). Admitted on account of vomiting and abdominal pain for 3 weeks with anorexia, constipation and flatulence, and noticeable loss of weight during the past year.

Past history of diabetes and hypertension for 4 years.

Examination showed cardiac enlargement. Blood pressure was 240/110; epigastric tenderness present.

Investigations.—Fractional test meals normal acid curve. Blood sugar curves diabetic type with a fasting sugar 252 milligrams per cent. Radiograph of chest showed left ventricular enlargement with aortic atheroma. Lungs clear. Barium meal showed a small gastric ulcer on the middle of the lesser curve posteriorly.

Progress in hospital.—There were intermittent bouts of vomiting becoming more severe, with alternating diarrhoea and constipation and colicky umbilical pain, together with gradual increase of abdominal distention. There was no tenderness or rigidity and bowel sounds were exaggerated during attacks of pain.

Autopsy.—(relevant findings) Heart. The left ventricle was slightly enlarged. There was gross atheroma of the thoracic and abdominal aorta. The stomach showed no active ulcer. The duodenum was congested, increasingly so until the jejunum was reached. All the small intestine, the caecum and ascending colon with first part of the transverse colon showed early signs of haemorrhagic infarction. The descending colon and rectum were normal. The superior mesenteric artery was completely occluded for about 4 centimetres with an old white organized thrombus. The coeliac axis was occluded by a large atheromatous plaque on which recent thrombus had occurred, spreading into the lumen (Plate I). Other branches of the aorta were normal. The pancreas was fibrotic.

Comment.—In this case complete occlusion of the superior mesenteric artery must have existed for weeks or months. With additional slow occlusion of the coeliac axis by thrombus formation, bouts of abdominal colic ensued with final infarction of the small intestine. This series of events strongly suggests that the collateral blood supply from the coeliac axis had been maintaining the small

which showed purple discoloration commencing with the transverse colon some 3 inches proximal to the splenic flexure and extending to the end of the sigmoid colon The rectum appeared congested

Abdominal aorta —An old standing ante mortem thrombus extended from just below the renal arteries down to the bifurcation of the aorta on into both common and external iliac arteries terminating in the femoral arteries on both sides The distal aorta was completely blocked A saccular aneurysm about 1¼ inches across involved the mouth of the inferior mesenteric artery which was completely occluded by thrombus for its first inch until it divided into its sigmoid and left colic branches (*see* Figs 10 and 11) The arterial walls appeared normal No thrombosed veins were found

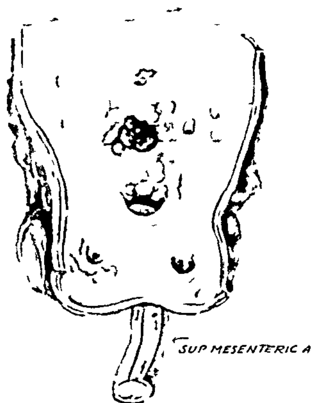


FIG 11 —The appearances of a barium enema in the presence of inferior mesenteric infarction The haustration of the descending and distal half of the transverse colon has disappeared (Case Ref 3232/47)

The mucosa of the ascending colon was ulcerated From splenic flexure to rectum the mucosa was necrotic and stripped off In the rectum ulceration similar to that in the ascending colon was found

Comment —The resemblance between the symptoms in this case and ulcerative colitis are striking Both barium enema and sigmoidoscope showed appearances resembling ulcerative colitis However the aneurysm formation at the mouth of the inferior mesenteric artery and the organized state of the thrombus in the artery provided the evidence of primary vascular disease

Thrombosis of the aorta is described as a complication of ulcerative colitis The appearances in this case raise the possibility of the vascular factor being primary and not secondary in some instances of such ulceration Such a factor



The abdominal aorta from behind showing complete old white occlusion of the superior mesenteri artery Above it is seen the mouth of the coeliac axis surrounded by gross atheroma on which there *has been recent thrombus formation (Case Ref* 3979 48)

intestine—and that when this ceased gangrene of the bowel occurred The occlusion of the superior mesenteric artery had produced no symptoms except perhaps loss of weight

Chiene (quoted by Welch and Rolleston 1909) described a more striking case in which there was found at autopsy complete obliteration of the coeliac axis and both superior and inferior mesenteric arteries with an adequate collateral circulation established through greatly distended extra peritoneal anastomosing arteries

These cases show how greatly viability of the gut after mesenteric arterial occlusion depends on collateral circulation which in its turn depends mainly on the degree of reflex vaso dilatation or spasm There is no doubt clinically and experimentally that such collateral circulation is aided by intravenous papaverine hot packs procaine injection into the mesentery and oxygen administration all being measures designed to relieve vaso spasm and anoxia

The contrasting picture of infarction of the gut with partial occlusion of the superior mesenteric artery is illustrated by the following case

H C male aged 47 years (2727/47) He had a past history of rheumatic fever at the age of 14 years For 3 years he had complained of intermittent attacks of epigastric discomfort which during the last few months had become more severe and accompanied by vomiting which gave relief He had about 2 such attacks a month He was admitted with signs of intestinal obstruction vomiting and severe abdominal pain Examination showed a grossly emaciated dehydrated man with mitral stenosis The abdomen was soft with only slight epigastric tenderness The patient died suddenly after a few hours

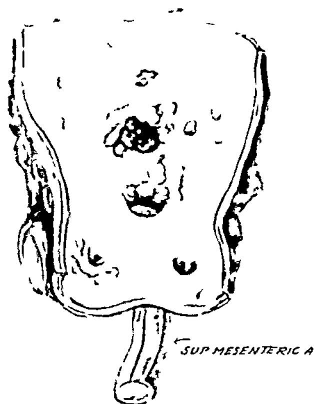
Autopsy showed mitral stenosis of severe degree with a very large left auricle containing a large ante mortem thrombus Liver and spleen were normal The stomach was grossly dilated The whole small intestine was plum coloured with a haemorrhagic mucosa It was in a condition considered to be viable The large gut was normal The abdominal aorta showed gross flaking and splitting of the intima At the bifurcation there was thrombosis which partially occluded the right common iliac artery The mouth of the superior mesenteric was partially occluded by a thrombus which lay deep to a split in the intima (Fig 12) This appearance strongly suggested its origin from a subintimal haemorrhage as described by Wartman (1950) Histological examination of both the mitral valve and the aortic wall showed no evidence of cellular infiltration It is therefore not possible to say whether the peculiar condition of the aorta was due to rheumatic arteritis or not

The case is cited in order to lay stress on (*i*) the long history of abdominal pain and vomiting (*ii*) that partial occlusion can produce gross gut ischaemia and (*iii*) the association of this type of mesenteric vascular disease with rheumatic carditis

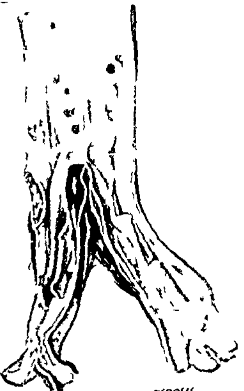
Splanchnic vascular spasm

Though the importance in physiology and pathology of the splanchnic blood supply is apparent it is only of recent years that methods for investigation of its variations have begun to be available

Such work as that initiated by Trueta and others (1947) first demonstrated experimentally in animals how gross may be the splanchnic vascular adaptations to stimuli occurring in distant parts of the body



The abdominal aorta from behind showing complete old white occlusion of the superior mesenteric artery Above it is seen the mouth of the coeliac axis surrounded by gross atheroma on which there has been recent thrombus formation (Case Ref 3979 48)





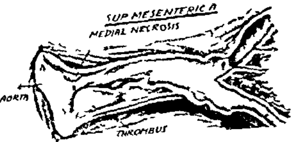


FIG 12 —Medial necrosis with subintimal thrombus formation On the left is shown the appearance at the bifurcation of the aorta On the right above is shown the early gangrenous appearance of the small gut below the partial occlusion of the superior mesenteric artery at its origin from the aorta by thrombus formation commencing subintimally in a patch of medial necrosis (Case Ref 2727/47)

In these experiments the mesenteric artery changed calibre in an opposite manner to the renal artery almost constantly With a large dose of adrenaline hydrochloride and marked hypertension the renal and femoral arteries showed intense constriction whilst the thoracic and abdominal aorta showed gross dilatation and tortuosity with dilatation of the mesenteric artery

With stimulation of the sciatic nerve by faradic current or by tourniquet application to the leg the renal arteries constricted whilst the mesenteric artery remained unaltered or dilated The same stimuli after section of the splanchnic nerves failed to produce constriction of the renal arteries and the mesenteric artery remained unaltered

Decrease in blood volume by bleeding produced uniform constriction in both renal and mesenteric arteries proportional to the amount of blood withdrawn

These experiments clearly show the sensitivity of the mesenteric artery to nervous or chemical stimulation response being usually in an opposite manner to that of the renal arteries except with fall of blood volume

The mechanism of the Oxford Shunt for the kidney may also apply to other organs In the case of the stomach *suggestive evidence has been obtained by* Barclay and Bentley (1949) at operation for partial gastrectomy that such a shunt is created by the abdominal incision following which there is a rapid increase in oxygen saturation of the blood in the veins of the stomach In the resected portion of stomach the mucosal arterial twigs could not be injected whilst they were patent in stomachs from normal cadavers

Evidence that such shunts may be active physiologically is produced by Prinzmetal and others (1948) who found that glass spheres 20–40 times the diameter of normal capillary lumina all passed through the hepatic and splenic circulation in various animal experiments

The occurrence of a vascular shunt presupposes a distal region of vaso con striction Abell and Page (1946) have shown in the rabbit that both mesenteric arteries and veins are sensitive to angiotonin or renin the vaso constriction being accompanied by vigorous peristalsis

That increased peristalsis or spasticity of the intestinal muscle is an early accompaniment of ischaemic anoxia has been shown in experiments on strangu lated loops of gut in the dog by Laufman and Method (1947) Later there is secondary arteriolar relaxation with venous engorgement Release of the strangu lation in the early stage resulted in a reactive hyperaemia similar to that which occurs in limb vessels

As in limb arteries spasm of the splanchnic vessels is a governing factor in defining the extent of ischaemic changes following occlusion of an artery and this in two different ways First the site of lodgement of an embolus is decided as much *by the calibre of the vessel as the size of the embolus An embolus held up by* spasm of the vessel wall may pass far towards the periphery when such spasm is relieved Secondly as emphasized so strongly by Leriche (1940) and also shown in the experiments of Trueta and others (1947) reflex vascular spasm following occlusion extends chiefly peripherally throughout the part of the vascular tree in volved but may reach proximally as well In this way a greater length of bowel may be deprived of collateral circulation than that supplied by the occluded artery

Increasing attention is being paid to the occurrence of ischaemic necrosis of

kidneys spleen and small intestine without evidence of occlusion of the arteries to the infarcted areas The peripheral vaso-constriction needed to maintain blood pressure and local reflex changes occurring in states of shock may be responsible

An instance of this is described in a case of sickle cell anaemia by Kimmelstiel (1948) where multiple foci of ischaemic necrosis were found in kidneys liver gall bladder and brain without thrombotic occlusion of the arteries He suggests that thrombosis when it occurs may be due to secondary arterial dilatation at which time anoxic changes in the arterial walls together with stasis condition the process

This view is also supported by Campbell and Henderson (1949) in a study of symmetrical cortical necrosis of the kidneys in infants in which condition the frequent incidence of haemorrhagic infarcts of the oesophagus stomach small intestine and colon have been described Though such lesions may be regarded as secondary to uraemia they point out that the necrotic areas may be patchy or as gross as any massive haemorrhagic infarction Focal necroses in the liver have also been reported—and the hepatorenal syndrome is well known They suggest a concept of a syndrome of splanchnic vaso spasm producing these lesions

The reciprocal relationship that of intestinal distension producing the renal shunt has been described in experimental work in animals

Hypertension and the splanchnic vessels

Though the burden of hypertension is most often expressed in the coronary cerebral and renal regions of the arterial tree the effects in the coeliac and mesenteric arteries are worthy of the increasing attention they are receiving

In experimentally produced hypertension lesions in the intestinal arteries have been commonly noted

The experimental work of Selye (1950) in the production of hypertension in the rat by deoxycortisone a corticosteroid which occurs normally in the suprarenal cortex shows widespread arterial effects The changes in the arteries resemble those of polyarteritis nodosa that is fibrinoid necrosis—a change that can be reversed by the gluco corticoid cortisone or adrenocorticotrophic hormone of the pituitary Gross changes in the mesenteric branches to the small intestine are seen as also in the pancreatic and gastric arteries

Similar changes are found in clinical cases of malignant hypertension In the pancreas necrotic foci were found by Pagel and Woolf (1948) in the presence of such arterial changes and thrombosis They emphasize the absence of fat necrosis in their case In other reported instances this has also been a feature as has the absence of symptoms referable to the pancreas Such infarction of the pancreas is a condition to be contrasted with haemorrhagic pancreatitis

In hypertension due to chronic glomerulonephritis the pancreatic arteries are similarly affected by fibrinoid changes and in this condition too widespread necrotic foci in the pancreas have been found In all these cases findings have been incidental no pancreatic disease having been suspected Such investigations as serum amylase or lipase have not therefore been carried out

The gastro intestinal vessels are said to be involved in 10–15 per cent of cases of hypertension When malignant changes occur arteriolonecrosis with involvement of the gut wall is not rare No known symptoms are produced by mild vascular

changes and in those with infarction with perforation or haemorrhage the picture is usually terminal The similarity between these changes and those of polyarteritis nodosa in which disease abdominal symptoms are common raises the question of aetiological relationship into high relief

Spontaneous intra abdominal haemorrhage

This rare event has a diverse aetiology Three main factors are responsible hypertension pregnancy and congenital aneurysms

Many of the reported cases have occurred in pregnant women near full term often in the presence of hypertension The site of the haemorrhage in this group is often unascertainable owing to the large amount of clot and destruction caused by its spread The large majority are however retroperitoneal in origin most occur in the upper abdomen burst through into the lesser sac and so into the general peritoneal cavity

In some cases the source is perirenal Such perirenal haematomas may arise from suprarenal infarction as in a case operated on by Corcoran and Strauss (1924) Spread across the abdomen behind the lesser sac and down into the pelvis may freely occur Though in proved cases of suprarenal infarction such spread has not often been found (Keele and Keele 1942) this source was considered probable by Woolf and Thomson (1949) in a case in which haemorrhage extended from the right suprarenal region to the left splenic flexure It is common for the region of the suprarenal to be destroyed too thoroughly to be sure of its being *the site of origin*

Gillam (1948) comments on the frequency with which the splenic artery is responsible for spontaneous haemorrhage This artery seems particularly liable to rupture without hypertension and it is of interest that it is the commonest artery in the abdomen to show gross histological changes in its wall in non hypertensive cases It is also a frequent site of aneurysm formation These are commoner in women than men and like congenital aneurysms in the subarachnoid region tend to rupture with the advent of hypertension This is perhaps the factor that increases the risk during the last weeks of pregnancy though other splenic changes may be responsible

If at laparotomy haemorrhages are found in the mesentery with diffuse ecchymosis over the peritoneum it is wise to consider the possibility of atypical scurvy In such cases there has been very satisfactory resolution of the condition post operatively following saturation of the patient with ascorbic acid

REFERENCFS

Abell R G and Page I H (1946) *Am r J med Sci* **212** 166
Apley J (1949) *Proc R Soc M d* **42** 918
Baer S and Ioewenberg S A (1948) *Gast oenterolog* **10** 617
Barclay A D and Bentley F H (1949) *B it J Radiol* **22** 6
Barrett N R (1946) *Thorax* **1** 48
Bayford D (1789) *Mem Med Soc Lond* **2** 71
Bedford D E and Parkinson J (1936) *Brit J Radiol* **9** 776
Bockus H L (1946) *Gastroenterolog* Vol 3 594 Philadelphia and London Saunders
Campbell A C P and Henderson J L (1949) *Arch Dis Childh* **24** 269
Carter A B and Maclagan N F (1946) *Brit med J* **2** 80

REFERENCES

Casman J (1947) *Acta clin belg* 2 113
Corcoran W J and Strauss A A (19.4) *J Amer med Ass* 82 676
Correll H L and Lindert M F (1949) *Amer Heart J* 37 446
Cunninghame G J (1949) *B it med J* 1 1075
Dock W (1949) *J Amer med Ass* 140 1135
Ellis L B (1946) *Brit Heart J* 8 53
Gilbert N C Leroy G U and Fenn G K (1940) *Amer Heart J* 20 519
Gillam J F E (1948) *Brit J Surg* 36 03
Gross R F and Ware P F (1946) *Surg Gynec Obstet* 83 435
Gull W (1857) *Guy s Hosp Report* 3 311
Gullickson M J McRae J H and Campbell D A (1949) *Ibid* 89 153
Hines L E (1947) *Surg Gynec Obstet* 85 214
Hodge G B and Messer A L (1948) *Ibid* 86 617
Kahn M H and Barsky J (19 8) *Ann intern Med* 2 401
Keele D N and Keele K D (1947) *B it med J* 2 687
Kimmelstiel P (1948) *Amer J med Sci* 216 11
Kissane R W Fidler R S and Conn J J (1950) *Amer J med Sci* 219 48
Laufman J and Method H (1947) *Surg Gynec Obstet* 85 675
Leriche R (1940) *Pr med* 48 601
Loeffler W and Esselier A (1946) *Gastroenterol gia Basel* 71 75
Mckee F W Schloerb P R Schilling J A Tishkoff G H and Whipple G H (1948) *J Exp Med* 87 457
Mason S C and Pollard H M (1949) *Surg Gynec Obstet* 89 271
Master A M Dack S Stone J and Grishman A (1949) *Arch Surg Chicago* 58 478
Mendeloff A I Kramer P Ungelfinger F J and Bradley S E (1949) *Gastroenterology* 13 22.
Meyer W W (1947) *Virchows Arch* 314 62
Morrison L M and Swalm W A (1940) *J Amer med Ass* 14 217
Myers J D and Hickham J B (1948) *J clin Invest* 27 690
Olsen A and Clagett O T (1947) *Post Grad med J* 2 417
Pagel W and Woolf A L (1948) *B it med J* 1 447
Paul O Castleman B White P D (1949) *Amer J med Sci* 216 361
Prinzmetal H Orwitz F M Simkin B and Bergman H C (1948) *Amer J Physiol* 152 48
Rachmilewitz W and Braun K (1945) *Brit Heart J* 7 7?
Reichert F L Rytand D A Bu k E L (1934) *Amer J med Sci* 187 794
Report on Sprue in India (1946) *Army Headquarters Medical Directorate*
Rochet P (1947) *Lyon Chir* 42 63
Rothstein J L (1935) *Amer J Dis Child* 49 1578
Ryle J A (1948) *The Natural History of Disease* 2nd ed London Oxford University Press
— and Russell W T (1949) *B it Heart J* 11 370
Scholefield J (1949) *Ibid* 1 348
Selye H (1950) *Brit med J* 1 203
Simonson E Alexander H Henschell A and Keys A (1946) *Amer Heart J* 32 .02
Tennant R and Zimmerman H M (1931) *Yale J Bi l Med* 3 495
Thompson R B (1947) *Arch intern Med* 80 607
Trueta J Barclay A E Daniel P M Franklin K J and Prichard M M L (1947) *Studies of the Renal Circulation* Oxford Blackwell
Wartman W B (1950) *Ame Heart J* 1 79
Weiss S and Ferris E B (1934) *Arch intern Med* 54 931
Welch W H and Rolleston H D (1909) Embolism and Thrombos in *System of Medicine* Vol 6 p 691 London MacMillan
Woolf A L and Thomson H R (1949) *B it med J* 1 573

CHAPTER 3

A PSYCHIATRIC APPROACH TO DIGESTIVE DISORDER

DESMOND O'NEILL

A great step towards independence is a good humoured stomach —Seneca Epistles 123 3

PREAMBLE

The concept of disease as mal adaptation

THE movement of thought in medicine has added another meaning to the interpretation of disease We know now that it is not enough to look for an external noxa—a bacterium or a poison—or for a structural derangement We have also to ask in what way has the adaptation of this organism to its environment gone wrong? The spectacular advances of the last century in the physical sciences brought medicine out of its medieval twilight and provided new tools for the study of disease Biophysics and biochemistry opened the way to a new ordering of concepts of aetiology *Despite these great advances the behaviour of certain* disorders was left unexplained by the physical variables known to exist Now we recognize that to discover a germ is not to explain an illness that drooping of the viscera of itself does not cause symptoms unless the patient has some other reason for being ill There is much illness which cannot be properly understood unless we add another dimension to our knowledge of the patient—the manner of his adjustment to life and to himself For instance some at least of the relapses of duodenal ulcer are the physical expression of an emotional upheaval and if we are aware of this we can use our awareness for the patient s good This *principle can be epitomized thus mal adaptation can produce sustained emotional* tension which carries with it bodily changes at first functional and later structural

Somatic correlates of emotional states

The last two decades have seen a remarkable efflorescence of research into psychophysical relations In the early years this work contained much that was uncritical and speculative later experimental studies made under controlled conditions began to appear and now our knowledge in this field stands on the same base as the rest of medicine A great deal of the pioneer work has been carried out in the United States of America Marcussen and Wolff (1949) Mittelmann and Wolff (1943) and Ripley and Wolff (1950) for example have produced many sound and objective studies of the behaviour of bodily systems in conditions of emotional excitement The observations upon Tom a man with a gastric fistula are well known There is a good deal of evidence that other mucosal surfaces behave as does the lining of the stomach the mucosa of the bladder

the large bowel the vagina and the nose (Wolff 1947) There is scarcely an organ except perhaps the liver which has not been examined to find how it reacts in states of tension For example the tension of combat flying was shown to precipitate albuminuria (Ahronheim 1947) and the tension of domestic strife attacks of extrasystoles (Stevenson and others 1949) and of auricular fibrillation (Duncan and others 1950) There has been for 11 years a journal *Psychosomatic Medicine* devoting itself entirely to publications in this field alone and the river of writings on the adaptive disorders is now in full spate

The somatic effects of emotional excitement are not merely changes in function that are transient and reversible If we accept that emotional tension has a large influence in the precipitation of asthmatic attacks it must then be admitted that it is a principal determinant of kyphosis and emphysema If mal adaptation can predispose to ulcer it can predispose also to perforation

A genetic view of medicine

One chief growing point of research is the study of the disorders of childhood The horizon of the child is small and his environment known and therefore *controlled much more than is that of the adult* Moreover *his mental processes* are much more explicit and they may be readily followed by such techniques as play therapy To see the development of illness as reaction to stress in a child is to learn something of the origins of disease to help modify a morbid reaction pattern is to attack disease at its source

In this chapter the reactions of the gastro intestinal tract to stress are described under the headings of individual symptoms and patterns of illness It will be understood that these categories are not exclusive The final section contains a brief review of diagnosis and treatment

INDIVIDUAL SYMPTOMS

Vomiting

The child who vomits is often expressing quite plainly his defiance of unreasonable demands made upon him by adults and his refusal to comply with their wishes

A boy aged 10 years was brought to hospital because of attacks of vomiting He was born in Eire and was brought up there by grandparents who gave him considerable freedom He did well at school and was happy he enjoyed playing in the open country near his home At the age of 8 years he was brought to live in an urban tenement in London with his parents who were fairly strict He felt stifled in the city and was often punished by his father for slight offences At school he had difficulty with his work The school dinners compared very unfavourably with what he had been given in Eire and when he was made to eat the food he vomited

Sometimes the vomiting may be regarded as a conscious act of retaliation

A girl aged 3 years had vomiting attacks regularly after being punished Her mother said If I get cross and smack her she ll cough and then vomit It s deliberate She would also vomit if she was pressed to swallow solid food which she did not want

In adults the retributive quality may not be so manifest but this form of vomiting is by no means uncommon

A man aged 27 years was in hospital for investigation of a duodenal ulcer His pain did not clear up with rest in bed and he was observed to be vomiting several times a day it was thought that operation might have to be considered The patient was a gay restless fellow who craved for variety he could not tolerate being confined to his bed and he greatly resented the ward discipline I suggested that he should be allowed to be up and about to sit by the fire and gossip with other patients As soon as he was released from restraint the vomiting stopped

The element of resentment seems to be the most important single factor in the emotional field which enters into the causation of vomiting It may be possible to witness the transition from physical symptom to behaviour disorder

A boy aged 12 years responded by vomiting when his parents would not do as he wished At my suggestion they tried the effect of giving him more leeway and did not thwart him more than they could help Except for one minor attack he did not have any further vomiting but he became fractious and troublesome had violent tempers and shouted at his mother

The timid person who cannot summon up courage to hit back in word or deed when he is attacked may have a vomiting spell when the quarrel is over the effect is the same when a restraint is imposed upon direct action by feelings of affection or respect Thus a patient was sickened by the continual advances made to him by an over amorous wife when these had been going on for some months he began to vomit soon after entering the house Here the symptom takes the place of a gesture of disgust or rejection

Graham (1951) who has made an extensive study of the subject believes that the so called cyclical vomiting of children is a form of stress disorder The two main precipitating causes of attacks are emotional upset and mild infection usually of the upper respiratory tract Of these the former is much the more important and is easily overlooked Trouble at school scolding at home the excitement of parties and such like often precede the onset of the attack

The psychological significance of vomiting attacks can as a rule be discerned without much special investigation yet one may feel sure that the symptom in a certain case is psychogenic without being able to define the precipitants The patient may have strong resistance to the idea that his illness has any emotional meaning and vigorously oppose the interpretation of it in these terms An attitude of bland indifference or euphoria is not uncommon

I have on occasion seen vomiting behave as migraine so often does that is to appear the morning after a day of particular stress In such a case there may be headache as well and the syndrome is perhaps then to be considered as akin to the migrainous attack There is no doubt that vomiting can occur where migraine would be expected for example in the perfectionist person when he is laden with many affairs Rarely it follows with an interval upon other types of stress such as the anxiety of combat flying

Pregnancy is attended by vomiting in many women who are consciously or unconsciously rejecting maternity Vomiting in pregnancy is one of the series of symptoms which I have named the Atalanta syndrome after the Greek goddess who competed so successfully with men I believe that in some cases at least the nucleus of this syndrome is an unconscious repudiation of femininity Vomiting in this setting is singularly resistant to medical treatment the patient is likely to have difficulty in the handling and rearing of her children

Dysphagia

When difficulty in swallowing cannot be explained as an organic dysfunction it is worth while to look into the circumstances in which it appears

A woman aged 37 years was referred for an opinion She said that the muscles of the throat are tight she had no appetite and food sticks in the throat The symptoms came on in December in October her husband was offered a new and better job out of London and decided to take it She was glad for his sake but reluctant to move house In December he went to the country and took up his post The patient said I didn t realize till then what it meant she felt aches and pains in the throat and a sense of obstruction She was investigated in hospital and an oesophagoscopy performed no physical cause for the dysphagia was found In talking over the move and the uprooting of her social and working life in town she wept once or twice then brightened up and said that after all the new post was a promotion and was good for them both At the second visit the dysphagia had gone

This case illustrates (a) the psychogenesis of a physical symptom the patient discussed the move with her husband and accepted it in her conscious mind but the onset of symptoms when he left home showed that she rejected it emotionally and in fact would not swallow it (b) the ventilation of feeling during the exploration of this theme and (c) disappearance of the symptom when the patient felt better able to adopt a different attitude to the change in her life

Conflict in the sexual field often manifests itself by gastro intestinal symptoms among them dysphagia

A woman aged 35 years complained of difficulty in swallowing pains in the abdomen and back and headache She married at 28 years intercourse was never very satisfactory and she felt no relaxation after it Her husband went away on military service when their child was 10 days old while away from home he experienced sexual tension and on his return was much more eager for coitus than his wife The patient said he was too quick left me in the air She lost all taste fo intercourse and told her husband she couldn t face it The symptoms appeared at this time and she then didn t feel well enough for it This defence was successful for 18 months one attempt at intercourse made her terribly sick for three days She told her story with a bright vivacious air and her symptoms clearly caused her no distress As a girl she was regarded as a tomboy and her mother often said she should have been a boy Her ambition was to work in an office after school she took a job as a cashier and stayed at it losing as little time as she could at the child s birth She told me that intercourse was never the same after the girl was born

In this patient the onset of dysphagia coincided with inability to tolerate intercourse and the symptom had an obvious function in her mental life of which she was wholly unaware she showed very well the complacency and satisfaction of the hysterical person with her symptoms The dysphagia here seemed to signify refusal to accept the risk of conceiving again and so interrupting her career and beyond that a repudiation of the female role which is often associated with gynaecological disorders (O Neill 1950)

Over eating

Eating is a simple and primitive way of wringing comfort from a hard and unsympathetic world This mechanism illustrates perhaps better than any other

how the child in us lives on and indeed in time of crisis takes control of our actions

> A girl aged 30 years a refugee worked as a barmaid in London She had no real friends and no accessible relative except a mother who looked on her coldly When desolation and self pity surged up within her she would go round to the snack counter and eat a sandwich This allayed her distress for a time

Though this kind of eating may be recognized as purposeless and even disagreeable it has a compulsive irresistible quality

> A woman aged 28 years was referred because of psychogenic menorrhagia She had nursed her husband through a lengthy illness during which she had endured abuse and ill treatment at his hands When he died she was left alone with a small girl and little money She had to work at an uncongenial job to keep herself and the child After the child went to bed in the evening as she sat alone in the flat thinking of the past she would be seized by an uncontrollable urge to eat all the food there was in the larder At the end of an orgy of eating she felt uncomfortable and would sometimes vomit

This non nutritive function of eating is seen in pure form in children Both in them and in adults if it is continued obesity may follow (*see* page 65)

Under eating

A mother will complain that her child eats nothing though he is cheerful and active and plainly quite well Her statement means that the child does not eat what he is offered and he is probably offered too much Here the body is deciding for itself and rightly how much it wants

A refusal to eat is one of the two main signs of negativism and resistance to coercion in young children the other is refusal to excrete when the mother wishes it It is rare for such under eating to become of grave concern Where the parents have whimsies about what they will and will not eat the children usually have them too The depressed child may turn from his food he may on the other hand over eat

Rose (1943) has given a classification of children with anorexia (a) The children are rejected by their parents These children may be found in the care of an agency or abandoned (b) The parents are dominated by fear which is shown to the child as aggression or doubt over exacting feeding schedules or doubt about the choice of food Many simple feeding problems are the outcome of parental over concern (c) The parents are deeply neurotic The parent who is filled with wanting cannot give true support to the child Refusal to eat in the child who is resisting its parents is the germ of that form of anorexia in the adult which is a resistance to maturation and adulthood

In states of depression loss of appetite is generally found if it is looked for Lack of inclination for food is part of the diminished zest for life in the anxiety states with depression which crowd our surgeries and out patient clinics it is a regular but not a presenting symptom and the loss of weight which it entails is *not great Only when* the refusal of food is stubborn and protracted does the consequent inanition become a serious matter and then it can be serious indeed (*see* anorexia nervosa) Everyday loss of appetite does not need treatment in itself it is a reflection of the mental state and will recover when that does

Abdominal pain

As far as my experience goes in both adults and children abdominal pain is a common mode of expression of emotional disharmony Although I was familiar with it as an isolated symptom and as one component of nervous dyspepsia in the adult I did not realize how common it was in children until I had the opportunity of investigating a consecutive series of children attending a paediatric clinic with recurrent abdominal pain as a presenting symptom (MacKeith and O Neill 1951)

All the 25 children in this series age range 3-16 years were physically examined and in none was there any obvious physical cause for the pain I made a careful psychiatric appraisal of each child and tried to establish the pathogenesis of the symptom drawing upon knowledge gained from teachers reports and from repeated interviews with a parent usually the mother In 4 children the causation of the pain remained quite obscure In 6 I felt sure that emotional tension was one contributory factor or determinant among others in 7 it was probably the main determinant and in 8 emotional tension seemed to be the dominant factor That is in 15 children or more than half of the whole series emotional tension was much the most important variable to be reckoned with Of the 21 children whose attacks were associated in some way with stress 17 had other tension signs headaches poor sleep bad dreams fidgets tics stammering disorders of behaviour and other similar things In other words the abdominal pain in the majority did not stand alone but was part of a general syndrome of mal adaptation A history of nervous disturbance or stress disorder was found in one or both of the parents in 14 cases In the group of 15 children m ntioned above the correla tion of attacks of pain with a particular situation was clear Anxiety and fear were the commonest emotional states associated with the pain in 17 of the 21 cases In 3 anger seemed to be the most important and in 1 grief The two principal sites for the pain were the umbilical zone (12) and the lower abdomen (7) Severity varied from mild twinges to quite severe spasms in which the child might double up and become pale In 7 cases vomiting occurred in some attacks I was able to treat 16 children at some length In 3 the symptoms went on as before 6 w re improved and in 7 the attacks of pain cleared up and the child seemed generally better In many children it was possible to verify my hypothesis about the origin of the pain for exampl the attacks diminished considerably in one child directly after she had begun to show violence to the puppets at play therapy and to do to them what she would have liked to do to her own parents

The emotional determinants of pain in duodenal ulcer are considered elsewhere In adults the complaint of abdominal discomfort or pain apart from ulcer is very often to be interpreted in emotional terms Its physiological basis may be clear enough

A girl aged 19 years was admitted to the surgical ward with a tentative diagnosis of intestinal obstruction She had had 3 operations in the previous year for the in vestigation of abdominal pain but nothing significant had been found In the ward it was noted that she readily became alarmed if she felt any pain at all and during an attack of pain loud borborygmi could be heard over the abdomen. I concluded that she probably had a slight degree of intestinal block or delay to the mild spasms of pain which this caused she over reacted violently with acute apprehension and

contraction of the gut with colic She responded at once to strong reassurance and simple suggestive measures Over a follow up period of 18 months she had no further severe attacks The onset of pain had followed a blow in the midriff which frightened her and she had always been liable to diarrhoea in states of excitement

Burning or aching epigastric pain seems to be associated in the main with discontent It may bring with it belching and vomiting or regurgitation of food and if a skiagram is taken *pylorospasm may be seen It is probable that with this* kind of pain the state of the gut is like that described by Wolf and Wolff (1943) as a reaction of resentment

A woman aged 32 years complained of feeling ill all the time epigastric discom fort belching stomach cramp headache pain in the back and loss of appetite She said that on trying to eat bread lumps of it come back She was dissatisfied with her flat and much irritated by a noisy neighbourhood Her two children won t obey they get on my nerves I get excited worked up She would not punish them as she had herself had a hard childhood (I wouldn t do it to them) but resentment was always boiling up Her condition improved quickly with simple treatment and the abdominal pain vanished

The chronic invalid often includes among his woes a complaint of abdominal pain he usually has many other symptoms as well The physiological substrate of this pain is as a rule obscure and it is to be regarded I think in most cases as of central and not peripheral origin

Diarrhoea

Diarrhoea has been described as a reaction of defeat and I have encountered it under battle conditions in men who were striving to do what was required of them in the face of increasing internal disruption by fear In such people the symptom is a signal by the body that it has had enough conscious fear might be conspicuous by its absence Persistent diarrhoea is found in some timid and inadequate individuals when they are struggling with circumstances which they cannot handle

A man aged 40 years attended hospital over some years with frequent loose motions which varied between 5–8 a day He was a native of Eire who was employed by one of the municipal authorities as a roadsweeper He was a tense passive rather dull and helpless man who for most of the time he was under observation by me lived in a single room with his wife and two children His wife upbraided him for not pro curing better accommodation for the family and he suffered greatly under her taunts but could not succeed in finding anything better or in getting another job at higher pay

Events which provoke apprehension may in the timorous child be followed by a spell of diarrhoea *and this may be repeated*

A boy aged seven years had recurrent attacks of diarrhoea lasting a week or two in each attack the bowels moved 4–5 times by day but not by night He was described by his mother as A happy child nervy a dreamer self conscious gets easily worked up nervous of doing anything frightened at school He got an attack after being bullied by a bigger boy at school and another after a family squabble at home Both father and mother tended to have loose motions if they were upset

The excitable restless mercurial child may have attacks of diarrhoea in situations arousing excitement

A boy aged eight years was brought to hospital by his mother with the story that he would run home from school in great haste and get very excited if he was not let into the house the moment he arrived While running, he might feel a spasm of abdominal pain and if he had to wait at the door he regularly soiled himself by the involuntary passage of a fluid stool

A patient who has had ulcerative colitis may come under observation because of chronic diarrhoea the emotional element in the pathogenesis of this state is then of the same nature as that which contributed to the causation of the colitis (*see* page 67)

Diarrhoea can signify impotent rage as well as helplessness and the bold and self assertive person who is thwarted by the obstinacy and ill will of others can demonstrate his anger in this way Diarrhoea and vomiting as two forms of response to frustration can exist together in the same individual

What is reported by the patient as diarrhoea may be no more than the frequent passage of small stools and this is sometimes the pointer to an intense pre occupation with the excreta one sign of hypochondriacal self-concern in obsessional people

Constipation

Some degree of constipation is usual in states of depression as part of the general lowering of bodily tone In severe depression the patient may come to believe that his bowels are blocked up and I have often heard the inmates of mental hospitals say that they have not had a movement of the bowel for some years It is I think a deeply rooted belief in people of our culture that the contents of the lower bowel are evil and must be got rid of at least once a day If the clearance is delayed the patient is seized with anxiety amounting som times to panic as the days go on in desperation he tries first one and then another pur gative There is then present in him the nucleus of the dep essive delusion of total constipation This state of blockage" has for the layman a very ominous meaning which is probably derived from a childhood training in regularity The bowel is one of the most important foci of hypochondriacal concern When there is any latent anxiety about its function the patient is apt to notice and remember advertise ments for special foods and proprietary purges which reinforce his conviction that a motion a day is essential to health and augment his hypochondriasis

For this reason many people suppose themselves to be constipated when they are not and visit the doctor in order to be given medicine to drive the evil out They are anxious about their bowel and it is the doctor s task to discern the real reason for their visit and to fasten his attention not on the bowel which is probably normal but on the anxiety *and to ask himself whence it springs* "Constipation in this setting has the same value as headache and the other screen complaints which patients bring it usually means that the patient is anxious about something but does not tell what that something is The current trend in screen complaints seem to be changing headaches and other bodily pains are common constipation less so

In children control of the bladder and bowel is one of the chief centres for the battle of wills between the child and his parents What the mother calls

constipation may be simple the child s quite reasonable refusal to pass a stool when she wishes him to When he does so refuse many mothers resort to force that is the use of a purge There is some ground for believing that the reaction patterns set up during the period of toilet training persist into later life and enter into the formation of character The child may utilize retention of faeces as a weapon for getting his own back and in such a case the condition which needs treatment is not his constipation but his mother s anxiety

PATTERNS OF ILLNESS

Compulsion neurosis with cachexia—anorexia nervosa

The central feature of the disorders grouped together under this title is a morbid attitude to food which ranges from simple loss of interest in eating to strong revulsion At one end of the scale the less severe disturbances of appetite are continuous with those described as under eating (*see* page 50) and the onset may be seen to follow a traumatic event

A girl aged 16 years (Lily) was admitted for investigation Her father was a nervous type who had suffered from indigestion all his life He had a haematemesis one night and was sent to hospital as an emergency admission a diagnosis of duodenal ulcer was made He was very ill for some time and an operation was performed Lily was shocked at the suddenness of his illness and worried about his condition. She began to feel sick looking at food could not eat and lost 2 stone in weight

At the other end of the scale there is difficulty with food which is more than mere anorexia

A girl aged 24 years (Susan) said I go through mental torture Food won t go down After eating I get terrific depression feel miserable Horrible feeling If I don t eat *I get awful pains I m always pre occupied with food have no release* I haven t lost my appetite

In this girl there was a desire for food but eating was associated with intense guilt and depression Though anorexia nervosa has remained the conventional title for a disorder such as this it is not in fact very appropriate since the nucleus is not absence of appetite but guilt The pathogenesis in these more severe dis orders is in my view complex and cannot be described in terms of a single conflict *It is true that fantasies occur in some at least of these patients which show clearly* the association which exists in their minds often at a deep level between eating and impregnation but this association is found also in other disorders and it cannot be the whole cause It seems likely that rivalry and hostility both inside and outside the family group can be diverted into the struggle over food which then comes to symbolize other and larger inter personal struggles

Susan said of her symptoms The fight about food goes on I know it to be crazy and infantile get worked up into a panic get hot worried nervous about eating My appetite is good but I can t admit it to myself I get hungry constantly want to nibble If Mother says she s hungry I lose my appetite at once I have quarrels with mother over food She described her mother as temperamental possessive strong willed kindly in a material way but no insight untidy and messy My feelings for Mother pull both ways At last there was a decisive battle Terrific upset mother said I must go said You re driving me mad I went to a hostel felt so free for a time seemed able to eat plenty without the old difficulty However away from home

she felt afraid Homeless and penniless and decided to go back At home the trouble with food began once more I felt the same feeling again

Susan s feeling for her mother was a mixture of affection and resentment and her conflict on this score was plainly linked to the conflict about food She was brought up as a perfect child never allowed to be naughty Dubois (1940) has proposed as an alternative title for anorexia nervosa compulsion neurosis with cachexia He described the typical personality as perfectionist rigid immature lacking in sex interest desiring approbation Dubois believed that the precipitating factor was often in the home situation parental over solicitude or subjugation aroused hostile feeling and therefore guilt in the child A more general hypothesis was put forward by Ross (1938) that resistance to feeding is one manifestation of resistance to growth no forward movement in growth is free from forces which oppose it He emphasized the importance of morbid attitudes in the parents for the pathogenesis of anorexia in children for example frank rejection of the child or the laying down of exacting food schedules In girls the onset of the menses represents an external force of growth driving the individual forward into an adult role anorexia nervosa often begins at the menarche

Rahman and others (1939) reported findings in 12 cases They were impressed by the reticence which the patients showed about sexual topics No history of mastur bation could be obtained most of the patients resented questioning especially about sex There was often a strong repudiation of sexuality and the results of starvation provided an excellent defence against establishing a love relationship All the unmarried patients feared physical love In 7 cases the anorexia was a secondary loss of appetite which appeared only after they had forced themselves to overcome severe hunger Most of the patients showed compulsive features of personality such as over-conscientiousness stubbornness neatness parsimony All had marked feelings of insecurity and were excessively sensitive seclusive serious and shy They had all been good children Social adjustment was poor In many cases the pattern of pre occupation with the gastro intestinal tract seemed to have been impressed on the patient early in life Once the symptom is estab lished the patient may find that by looking peaked and wan she can gain more sympathy and attention than she ever did when well this secondary gain may help to perpetuate starvation as an end in itself

The condition is much commoner is women Of Ryle s (1936) series of 51 cases 46 were women 33 of them under 30 years Ryle said that multiple causes were operating in most of his cases It has been argued that the psychological symptoms are secondary to a defect in endocrine development However the uterus of infantile form which is often found may be a consequence of failure in nutrition no ovarian deficiency can be shown in those who recover fully McCullagh and Tupper (1940) carried out a gonadotrophic hormone assay in 18 patients They found an excess in 7 and a measurable amount in 3 this was con sidered to be strong evidence against pituitary insufficiency The amenorrhoea may be regarded as of emotional origin Glucose tolerance in patients with anorexia nervosa according to Ross resembles that of simple inanition in his patients glucose tolerance curves returned to normal after feeding

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population at large has risen considerably (Craig 1948) It is a reasonable hypothesis that this increase is a consequence of the endemic anxiety and insecurity of our time Halliday (1948) in his book has put forward a case for regarding the upward trend of the psychosomatic affections as one of the symptoms of a sick society

An inquiry into the occupational incidence of peptic ulcer (Doll and Avery Jones 1951) has shown that it is more common in foremen and business executives who carry managerial responsibility and less common in agricultural workers than in the general population Anxiety over their work was more often complained of by those with proved duodenal ulcer than those with no dyspepsia this is held to be consistent with the view that men who are especially conscientious and careful about their work are more liable to fall victim to duodenal ulcer

Personality patterns in ulcer patients—The ulcer patient it has been said is more sensitive to rebuff and failure than his less ambitious and less active brother He may pass through life happily until some acute stress is suddenly experienced when his increased tension is likely to produce disturbance in the autonomic system and the gut He is reticent and feels things inwardly He tends to be restless keen proud in his work and intolerant of failure As compared with controls a group of ulcer patients showed more unreasonable fears and anxieties an inability to rest and abnormally fixed habits of life tension is a constant characteristic the ulcer patient is first and foremost a worker There is an urgent anxious and compulsive quality about his work and if he is not working he is worrying (Davies and Wilson 1937) Gilsenan (1946) found that his patients were reliable conscientious often over serious ambitious and self driving they could not easily relax Work was their only outlet and when they had to leave off work they attacked their leisure time pursuits with the same relen[illegible] the patients were neat and tidy and showed indecision a[illegible] Having to carry responsibility and deal with the unusual [illegible] than ordinary anxiety

There are many other studies in the literature of similar trend inference to be drawn from them clearly is that the ulcer patient by personality pattern is predisposed to react to certain stresses with which produces the changes in the gut leading to ulcer It is fair to that there is not universal agreement about the personality type de[illegible] Kapp and others (1947) examined 20 men with peptic ulcer and fo[illegible] conformed to this type Nine of the 20 had many of the traits psychopath and were openly parasitic towards their parents and Forces of the United States of America according to Berk and patients with peptic ulcer were seldom punctilious and [illegible] larger number were slovenly apparently placid unobtrusive From my own experience I am inclined to the view that there is sonality pattern for peptic ulcer or even for its subgroups but gastric and duodenal ulcer can and often do behave as adapti[illegible]

The effectiveness of treatment—It is characteristic of d[illegible] psychogenic component that during their history a great v[illegible] ments have been prescribed each of these has a phase of replaced by another The operative factor in them all is of

Treatment of the less severe case is straightforward Where the act of eating is highly charged with emotional meaning it may be most difficult and in the severe disorders the patient seems bent on suicide by illness In whatever form it appears *anorexia nervosa is a mental illness and should be dealt with as such*

Gastric and duodenal ulcer

Introduction

There are good grounds both physiological and clinical for regarding gastric ulcer and duodenal ulcer as distinct entities In many of the published reports however they are placed in the same category—peptic ulcer there have been for example numerous attempts to formulate a pattern of personality for the peptic ulcer patient This section contains first, a note on the evidence for considering peptic ulcer an adaptive disorder then a review of duodenal and of gastric ulcer and finally a summary of the material

Peptic ulcer as an adaptive disorder

Association of the illness with emotional tension —The most striking evidence of this association comes from the everyday experience of clinicians that the ulcer patient is likely to fall ill if he encounters a situation which arouses in him sustained emotional tension The emotional determinants of the onset of illness and of its relapses are certainly not manifest in every case Sometimes the patient is unaware of them or he may conceal them sometimes they cannot be established at all But they cannot be assumed to be absent if they have not been looked for

A man aged 39 years with duodenal ulcer gave a history of repeated attacks during his Army Service On being questioned about the cause of these attacks he at first *said he did not know of any and that they had nothing to do with parties or late* nights Later he admitted that his married life was far from happy and said his wife was peculiar disgruntled disappointed When he went home on week end leave she abused and attacked him unjustly and he felt hurt or bitter Ulcer pain came on regularly during the leave or immediately after it

Davies and Wilson (1937) showed that in 84 per cent of their patients with peptic *ulcer symptoms began soon after some event affecting the patient s work* his finances or the health of his family as compared with 22 per cent of a control series of patients with hernia Of 52 relapses proved by radiological examination 42 could be traced to some event causing anxiety to the patient They observed that failure on the part of the patient to relate ulcer symptoms to anxiety was *common In Great Britain* there was a sharp increase in the frequency of per*foration of peptic ulcer during the autumn of* 1940 and the spring of 1941 this was as Craig (1948) says the phase of the war in which its seriousness was brought home to everyone

Patterns of incidence of peptic ulcer —In the first 15 months of World War I the medical discharges from gastritis and peptic ulcer numbered only 709 whereas in the first 27 months of World War II the discharges from peptic ulcer alone were 23 574 (Tidy 1943) The maintenance or actual increase *in the death rate from* duodenal ulcer in all age groups despite therapeutic advances in the treatment of haemorrhage and perforation is strong evidence that the incidence in the

population at large has risen considerably (Craig 1948) It is a reasonable hypothesis that this increase is a consequence of the endemic anxiety and insecurity of our time Halliday (1948) in his book has put forward a case for regarding the upward trend of the psychosomatic affections as one of the symptoms of a sick society

An inquiry into the occupational incidence of peptic ulcer (Doll and Avery Jones 1951) has shown that it is more common in foremen and business executives who carry managerial responsibility and less common in agricultural workers than in the general population Anxiety over their work was more often complained of by those with proved duodenal ulcer than those with no dyspepsia this is held to be consistent with the view that men who are especially conscientious and careful about their work are more liable to fall victim to duodenal ulcer

Personality patterns in ulcer patients—The ulcer patient it has been said is more sensitive to rebuff and failure than his less ambitious and less active brother He may pass through life happily until some acute stress is suddenly experienced when his increased tension is likely to produce disturbance in the autonomic system and the gut He is reticent and feels things inwardly He tends to be restless keen proud in his work and intolerant of failure As compared with controls a group of ulcer patients showed more unreasonable fears and anxieties an inability to rest and abnormally fixed habits of life tension is a constant characteristic the ulcer patient is first and foremost a worker There is an urgent anxious and compulsive quality about his work and if he is not working he is worrying (Davies and Wilson 1937) Gilsenan (1946) found that his patients were reliable conscientious often over serious ambitious and self driving they could not easily relax Work was their only outlet and when they had to leave off work they attacked their leisure time pursuits with the same relentless fury As a group the patients were neat and tidy and showed indecision and scrupulousness Having to carry responsibility and deal with the unusual caused them more than ordinary anxiety

There are many other studies in the literature of similar trend to these The inference to be drawn from them clearly is that the ulcer patient by reason of his personality pattern is predisposed to react to certain stresses with undue anxiety which produces the changes in the gut leading to ulcer It is fair to say however that there is not universal agreement about the personality type described above Kapp and others (1947) examined 20 men with peptic ulcer and found only 6 who conformed to this type Nine of the 20 had many of the traits characteristic of the psychopath and were openly parasitic towards their parents and wives In the Forces of the United States of America according to Berk and Fredians (1944) patients with peptic ulcer were seldom punctilious and perfectionist by far the larger number were slovenly apparently placid unobtrusive and slow moving From my own experience I am inclined to the view that there is no common personality pattern for peptic ulcer or even for its subgroups but nevertheless both gastric and duodenal ulcer can and often do behave as adaptive disorders

The effectiveness of treatment—It is characteristic of disorders with a strong psychogenic component that during their history a great variety of physical treatments have been prescribed each of these has a phase of success and is then replaced by another The operative factor in them all is of course the patient s

faith in their efficacy This is usually dependent on his faith in the doctor who prescribes the treatment and on the doctor s own conviction of its value In the literature of the last 50 years on the treatment of peptic ulcer there are reports of 56 different regimes 89 drug preparations and 19 non pharmaceutical remedies (Cunha 1948) Probably all had their brief flowering of popularity Gill (1947) treated 20 ulcer patients with subcutaneous injections of distilled water and allowed them to smoke in 19 of the 20 the ulcer healed in 4–8 weeks The drug as Gill says is less important than the patient s confidence in the method

The evidence from physiology —Cushing (1932) observed that acute perforating lesions in the oesophagus stomach and duodenum in man occurred after operations for cerebellar tumour Stimulation of the parasympathetic centre in the diencephalon by intraventricular injection of pilocarpine or pituitrin caused an increase in gastric motility hypersecretion and vomiting the vomit ultimately contained blood Direct stimulation of the tuber is known to cause hypertonus of the gut particularly the pyloric segment

Wolf and Wolff (1943) in their now celebrated experiments on Tom a man with a gastric fistula demonstrated that emotional states were reflected in the behaviour of the stomach Pleasurable thoughts of eating were associated with increase in secretion motility and vascularity and an increase in all three accompanied anxiety hostility and resentment even when Tom had no intention of eating Fear sadness and kindred feelings—a reaction of withdrawal—were associated with a depression of these functions The length of time food remained in the stomach was much influenced by Tom s emotional reactions The threshold for pain and the occurrence of symptoms were found to depend on the condition of the tissues and thus indirectly on the emotional state These observations of course apply to one subject only and cannot be generalized Crider and his associate (1948) reported that their subject Doris showed depressed secretion and motility and blanching of the mucosa not only when fearful but also when she was considered to be angry resentful and anxious

An experimental study of gastric activity in patients with peptic ulcer was carried out by Mittelmann and Wolff (1942) During an interview with the physician records were made of the subject s speech and behaviour and also of the motility and secretion of the stomach and of finger temperature and respiration It was found that when anxiety resentment or guilt were stimulated during the interview there was almost always an increase in hydrochloric acid mucous and pepsin secretions Peristaltic activity became continuous and contractions increased in magnitude Respiration became more rapid and shallow and there was usually a drop in finger temperature Often in patients with ulcer pain of a burning or gnawing character was precipitated and increased amounts of fresh unclotted blood appeared in stomach extractions During and after interviews directed to increasing the subject s sense of security functional over activity decreased and approached the normal The changes in ulcer patients and in a group of normals were similar but the degree of over activity was greater in the former

Duodenal ulcer

The assessment of personality motives and attitudes in the adaptive disorders can be made by clinical and psychometric methods neither is wholly satisfactory

The former is bound to be in some degree subjective and although a test can be standardized there may be doubt about the interpretation of its results The Rorschach inkblot test is one of the projective methods that is the stimulus material is relatively unstructured and the images which the patient produces in his responses are in large measure a projection of his own mental content This test is open to the criticism that its interpretation depends on the experience of the user but it has the merit of probing beneath the surface of personality and providing some indication of the interplay of forces at a deeper level For this reason Kaldegg and I (1950) decided on its use in the examination of a consecutive series of 20 duodenal ulcer patients in 1948 Our results may be summarized as follows There was no predominance of any one personality type Two records with strong obsessional features and two with hysterical features were found but the remainder showed a wide range of personality pattern Thirteen of the records contained one or more signs of the presence of anxiety in evaluating these we had to make allowance for the natural anxiety of a patient with a chronic painful and disabling disorder but the anxiety was thought to be greater than what might be reasonably expected A failure to respond adequately to emotional stimuli was found in 10 of the 20 it seemed to us that this was the representation of a long standing difficulty in the handling of emotionally toned life situations and a tendency to the suppression of unpleasant feeling Emotional lability—proneness to thinking and acting impulsively—was shown in 8 records and signs of immaturity were seen in 12 To Card III in which human figures are almost always seen by normal subjects 7 of the subjects did not produce one human response this was interpreted as a sign of failure to achieve satisfactory relationships with other people In short the responses to the Rorschach test support the hypothesis that anxiety and a disturbance in the regulation of the emotional life occur more commonly in ulcer patients than in the normal though neither of these may appear on the surface No uniformity of personality type was shown in this series

Clinical study of the same series fully confirmed these conclusions Certain traits of personality were prominent among them were a strong need to go through with a job of work and a refusal to give up an inability to modify reaction patterns with changing circumstances vulnerability to certain forms of trauma notably blows to pride There were considerable variations in personality one patient was a gross hysteric who gave up at the least obstacle In general concern with money and position were the main preoccupations of male patients and concern with loss or absence of a love object of female patients this was not an absolute rule The dominant mental state could be described as anxiety and insecurity in 9 as grief or unhappiness in 4 and as resentment and frustration in 3 In the remaining 4 the psychopathology was in doubt While these states could often be traced to conflict at the ideational level such conflict was by no means the only mechanism of production Dysfunction at other levels of integration is equally capable of initiating prolonged emotional excitement For example one patient a man of 58 years had been throughout his life forceful energetic and aggressive with a tendency to irritability he had established hypertension which may perhaps be considered a concomitant of his emotional adjustment He had always experienced a strong drive to activity which he had as a rule

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Duodenal ulcer

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the dramatic section of the club and acted in their shows writing his own sketches He attended as an out patient for more than a year had no further attacks of dyspepsia and felt well

A man aged 25 years (Ralph) was admitted to a psychiatric clinic for treatment of a duodenal ulcer An investigation by dream interpretation and narco-analysis showed that he had serious and deep seated conflicts centred around his sexual orientation and his attitude to his mother He had strong passive homosexual needs which were repressed these disturbed his feelings for his wife and gave rise to sadistic impulses towards her which were rejected by his conscious self When the findings were reviewed it seemed at first unlikely that he could attain any satisfactory adjustment but he had some stabilizing factors in his personality and was of high intellectual level He stayed in the clinic several months and derived much benefit from group and individual psychotherapy After discharge he was seen at intervals Over 18 months he had only mild dyspeptic symptoms lost only one or two days at work and seemed much better

A man aged 60 years (Bob) with duodenal ulcer was referred to the psychiatric out patient clinic for supervision since it was felt that medical treatment alone was not enough He was the old soldier type tough proud independent and impulsive He had served many years with the Police and had then been discharged probably because he was regarded as unstable His wife was a feckless and unreliable woman who took all his money and gave nothing in return Bob made what money he could from odd jobs and refused to accept National Assistance as he despised charity His history showed that the exacerbations of ulcer dyspepsia were related in the main to disappointment and resentment at his wife s behaviour He attended the out patient department faithfully for 2 years and was given strong encouragement reassurance and support he took half a grain of phenobarbitone twice daily and set great store by it On this regime he kept well having one brief attack of pain during the whole period

Gastric ulcer

There have been very few personality studies of patients with gastric ulcer One of these is by Glatzel (1949) He concludes from a survey of 58 female patients that conflicts arising from occupational stress are less frequent in them than in men Striving for a goal which is impossible to attain and a feeling of being victimized and misunderstood are however common to gastric ulcer patients of both sexes In women an important source of tension is conflict from unfulfilled erotic desires

Hamilton (1950) compared 4 groups of 50 subjects each on their responses to a personality inventory (duodenal ulcer gastric ulcer non ulcer dyspepsia and controls) and made a careful statistical analysis of his results He found that there was a clearly significant difference between non ulcer dyspepsia on the one hand and the controls on the other in the sense that a group of traits dominated by anxiety dependence and guilt occurred in greatest saturation in the non ulcer dyspeptics and least in the controls The duodenal ulcer patients came fairly close to the former group and the gastric ulcer group about halfway between these and the controls This conclusion is consistent with the view that anxiety is associated with duodenal ulcer in nearly every case whereas in gastric ulcer it is a determining influence only in some

As far as I can judge there is the same range of personality pattern in gastric

been able to satisfy by absorbing it in heavy manual work As he grew older and vascular changes began to affect the integrative function of his nervous system he found that he could no longer get things done with the same efficiency and dispatch as in his younger days felt himself cramped and handicapped and grew much more irritable each wave of annoyance made itself felt as abdominal pain At another level disparity between ability and ambition was a fruitful source in these patients of long continued dissatisfaction At this level also may be considered the ill effects which follow from change of routine in a rather rigid personality The necessity to throw aside patterns of reaction which have become established through long usage and form fresh adaptations to a new situation may set up a condition in the organism akin to Goldstein s catastrophic reaction although in an attenuated form

The precipitating causes of ulcer pain in order of frequency were worry frustration and unhappiness Grief and self pity acted as determinants of pain in some cases This would seem to imply that Tom s gastric behaviour is not universal and that a reaction of withdrawal is compatible with an accentuation of ulcer symptoms Vomiting in association with annoyance and resentment was seen in a few patients The problem of localization—why did the patient fall ill with this disease?—could not be solved from the available data in 10 patients the family history was clear of any gastro intestinal disturbance Only 3 patients showed symptoms which could be classed as psychoneurotic In the great majority *(18) there was no evidence of hypochondriasis The life histories of these patients* seldom recorded gross hardships and deprivations The environmental situations associated with illness were such as are met every day without mishap by normal people it is the manner of reaction to the situation which is important In con clusion then the influence of emotional states on the course of illness in these patients was beyond doubt In many of them the illness had followed directly on an experience which set up an unusual and prolonged emotional reaction The type of reaction however was not specific and the production of an ulcer did not seem to be due in every case to factors operating at the mental level

If these views are correct the essential core of treatment in *duodenal ulcer* is to discover what attitudes in the patient are maintaining emotional tension which affects the gut and to work towards a new and more efficient adaptation The method of treatment must be flexible and designed to meet each patient s needs and there may be limitations imposed on it by physical disorder and by the patient s rigidity of personality Three examples are given below

A man aged 25 years (Sam) was admitted for investigation of duodenal ulcer Symptoms began during the war all his friends and relatives had been called up and had left home but Sam was exempted from military service as he had a shrunken leg the result of *poliomyelitis in early life This deformity had caused him to feel* inferior awkward and conspicuous and he was at ease only in the company of those he knew well When they went away he felt very lonely and melancholy and began to drink to comfort himself He noticed that stomach pains appeared only when he had been drinking On examination he was depressed felt isolated and aimless and said he had no one to talk to After a number of interviews devoted to exploring the background of the illness he was made a member of a social club Here he was well received made friends and found in himself a talent for clowning He joined

had engaged in advanced love making Doris was worried guilty and ashamed also annoyed that she had read my letters Food stuck in her chest and she vomited to relieve the discomfort which this caused Various treatments were tried repeated dilatations with a bougie anti-spasmodics and hypnosis none had more than temporary effect The hypnotist she said couldn t put me over She was kept under observation for some time in a psychiatric clinic Her mother was a tense worrying irritable person and it was found that although the superficial rapport between them was friendly Doris was harbouring strong but unrecognized hostile feelings towards her mother and considerable resentment about the way she had been brought up Further she had very mixed feelings about her impending marriage and a latent revulsion against sexual relations she was in fact sexually immature and did not seem capable of emotional growth She said that she could not think of marriage until she was relieved of the cardiospasm A sustained attempt was made to bring her to a realization of the meaning of her symptoms but this achieved nothing As an experiment she was then "ordered to suppress her daily vomiting and swallow her food normally She vomited much less after this injunction and appeared to have less difficulty in swallowing at any rate for some time but she became at the same time quite depressed irritable and abrupt and was rude to her mother and to Peter

This girl could not adapt the idea of separation from her mother to whom she had a strong though ambivalent bond and could not face a normal sex relationship Her personality was not well enough integrated to give up her illness and progress to a new adjustment When the symptoms were forcibly suppressed she passed into a depressive state This exemplifies the maxim that removal of symptoms in itself without an accompanying change in basic attitudes does no good and may even do harm

A girl aged 27 years was admitted to hospital for investigation Three years before while working for an examination she had noticed peculiar noises on swallowing like bubbles of air and had felt pain in the chest Food began to stick in the throat and near the lower end of the sternum. At school she had much preferred sport to work she played tennis and squash and captained the school team Her ambition was to be a professional tennis player Examinations were always a trial to her and she did not do well When the symptoms appeared she was preparing for a professional test and feeling apprehensive about the result tension got worse and worse She failed the test and had to sit again after several attempts she got through Other sources of tension had also been present she had a grudge against her employer for not recognizing the value of her work and would have liked to express her resentment openly but she could not I would go to pieces if I tried have to bottle it up When I saw her she had left that place of work and gone to another and the examination fever was over there seemed to be little tension left She was treated by mercury bougie and the cardiospasm went within a short time

In this case the emotional forces which had precipitated the disorder were no longer operating and the cardiospasm continued for a time under its own momentum Unlike the former case however the symptom yielded quickly to dilatation presumably because there was no emotional charge to keep it in being

Where cardiospasm is the bodily expression of strong pent up resentment as it often is psychotherapy can remove it at any rate in the early stage If the disorder has established itself or the patient is defending himself against the insight which treatment demands psychotherapy alone will not suffice

as in duodenal ulcer The diligent conscientious responsible person may develop a gastric ulcer, as may the erratic volatile hysterical one though I think the former is more likely to do so Gastric ulcer can appear for the first time in the setting of a tension producing situation and the association of relapses with emotional crises happens too often to be accounted for by chance This is not to say that gastric ulcer is an adaptive disorder in every case but in some cases it certainly is The reasons why this form of reaction to stress is chosen rather than another are not at all clear Since the emotional determinants of illness can be very similar to those in duodenal ulcer it is possible that a variation in the local conditions in the gut may account for the occurrence of one of these rather than the other

Summary

The presence of a demonstrable ulcer in the alimentary canal is so to speak an accidental finding what is important is the condition which precedes it This condition is not a disorder of the stomach and duodenum only but of the whole individual An understanding of the individual and his ways of reacting is essential if the pathogenesis of the ulcer is to be comprehended at all and is the keystone of rational therapy There is much that is puzzling about peptic ulcer for example the discovery of ulcers at necropsy in patients who in their lives have never complained of pain We can however be reasonably sure of this that both gastric and duodenal ulcer can behave as adaptive disorders Indeed it is probable that the latter seldom appears in any other role

Cardiospasm

Schindler wrote in 1927 Functional cardiospasm is always an organ neurosis which can be treated successfully in its early stages by psychotherapy The psychic disturbance is usually superficial The first serious complaints appear after a specific annoyance an annoyance that had to be swallowed usually caused by a superior Maingot (1949) 22 years later agreed that the onset often coincides with psychological trauma The cardia and lower oesophagus in some patients contract when they are depressed excited or angry He advised psychotherapy for the early and mild case but said it was of no avail for the established case

The best known formulation of cardiospasm as an adaptive disorder is that of Weiss (1944) The form of the disorder according to him is that of an organ neurosis the physical disorder symbolizes the unconscious conflict—it is a compromise between the gratification of certain impulses and their rejection by another part of the personality I cannot swallow this situation Weiss thinks that the psychological factor is not present in all cases and that there is a predisposition to which this factor is complementary The condition is usually found to arise at a moment of emotional conflict often during puberty in a patient whose early life shows evidence of personality difficulties Signs of neurosis or of adaptive disorder are frequently present in other members of the family

A girl aged 24 years (Doris) gave a 5 years history of difficulty in getting food down Some months before the onset her mother had found and read a letter from Doris s boy friend (Peter) she had construed this letter as an admission that the young couple

group of disorders is close to abdominal hypochondriasis There is general agreement among those who have had experience of it that the condition is recognizable as a psychiatric illness (Halstead 1946) Edwards and Copeman (1943) sent 101 of their 217 non ulcer dyspeptics to a psychiatrist on clinical grounds but only 2 of the 139 peptic ulcer patients These grounds may be stated as the character of the complaint the patient s bearing and manner and his history

In those I have seen much the commonest state of mind has been discontent fed up with my husband fed up with my wife fed up with everything I m cheated of happiness every time there s no fun in life Less often guilt is predominant Occasionally it may be possible to witness the transition from a complaint of dyspepsia to a complaint of mental symptoms I once saw a non organic dyspepsia change over quite sharply into a state of depersonalization Brief attacks of alimentary discontent which clear completely may attend a temporary frustration

This reaction form seems more likely to occur if the patient is handicapped in dealing with his problems by low intelligence and this is of course a hindrance in treatment though not a complete bar to it In the more intelligent therapy can be outstandingly successful

Obesity

Anxiety and weight increase

The body in a state of health regulates its own weight with remarkable nicety There are many influences which tend to alter weight such as variation in food and fluid intake and sweating yet if the subject is weighed every day at the same time the readings are constant within a 1 per cent margin (Dodds 1950) Very little is known about the working of this homoeostatic mechanism and the pathogenesis of simple obesity not due to physical dysfunction is by no means clear It is well recognized that a sudden gain in weight may follow an upsetting experience and in some obese children the sequence of events is quite clear

A boy aged 11 years (Peter) was referred for examination His height was 4 ft 11 inches and his weight 9 stone 10 lb An only child he was born in Belgium and lived there with his parents until 1940 His mother then came to England but his father refused to leave his business and stayed behind In 1945 the mother returned to Belgium to find that her husband had taken up with another woman She sent Peter to see his father hoping to win him over in this way but the attempt failed Peter said that his father was cold and did not want to see him he was hurt by this and felt depressed His gain in weight was noticed to begin at this time The only other symptom was headache Peter was described by his mother as very active full of life dances and sings She admitted that his appetite was bigger than average for his age and that she did not try to curtail the amount he ate She herself was also overweight

Over eating was the principal if not the only determinant of obesity in this case The pattern of Peter s response to stress was probably set by his mother who tried by eating to satisfy her own emotional hunger and emptiness

In their paper Shorvon and Richardson (1949) give several examples of sudden increase in weight after experiences arousing anxiety Greene (1950) has suggested

Abdominal hypochondriasis

The two main elements of this common condition are the complaint of in digestion and the complaint of pain or of unusual sensations in the abdominal area

A man aged 45 years complained of loss of appetite tiredness and dizzy spells a gnawing pain in the left iliac fossa a stabbing pain in the left flank and in the left lower chest and a dull sickly ache over the sacrum He had been off work for 2 months His wife said He talks of his pain all the time and complains all day He lies down *very readily Spends half his life in bed Can t walk Thinks his body is wrong Sits* and thinks of it Some time before this illness he had been in hospital for fibrositis and was then advised to take things easy not to do more than part time work and to lie down if he felt tired

A superstructure of hypochondriasis can be built up over any disorder in cluding the adaptive disorders although in some of these for example migraine and duodenal ulcer it is quite uncommon any illness can become valuable to the patient when it is utilized consciously or unconsciously for his own ends There is a large class of patients without demonstrable organic lesion who com plain of indigestion or pain or both and show a morbid and fascinated concern for their illness it is these who may be called abdominal hypochondriacs In trying to understand what is happening to them we come face to face with the crucial problem of pain When a man describes an aching in the epigastrium and is clearly under tension his gastric mucosa may very well be engorged and turgid and more than usually sensitive although we cannot be sure of this without looking at it his pain probably has a peripheral source and is comprehensible as part of the visceral concomitant of emotion However when pain is spread over a wide area is variable and flits from place to place it is not easy to conceive where a peripheral source could be and indeed such pain must be regarded as central in origin

The necessary conditions for abdominal hypochondriasis are a latent readiness to feel anxiety about bodily form and functioning and a precipitating event Illness in a relative a recent accident or illness in the patient himself are common types of precipitants another is the statement by a medical adviser that some organ or system is out of order As a rule though not always the patient has been before his illness self absorbed vain and demanding exceptions to this are found among those whose hypochondriasis is a sign of a depressive state

A long list of complaints and a querulous tone are useful guides in diagnosis The key is the patient s attitude to his disorder and sometimes this can be better appraised through the eyes of a relative In treatment the physician must above all things be tactful

Alimentary discontent

Under this head are those states of dyspepsia without ulcer and without prominent physical sign the patient has heartburn flatulence nausea fullness waterbrash discomfort here or there and he usually complains also of weakness headache fatigue palpitation dizziness and the like severally or together This

Eating occupies a special place in the psychic economy of many adults who are over w ight

The commissionaire at a well known restaurant (19 stone) told m that both his ambitions—to be a musician and to be a gentleman—had come to naught In fact he was a most amiable and courteous man and had some musical talent but since he could not play any instrument as well as he wanted to he did not play at all He enjoyed food It is the only solace I have

A girl aged 24 years (13 stone) a refugee from Europe was bored lonely and miserable in London If I m upset I must eat In her rare spells of contentment she felt little hunger The restaurant opposite her place of work was a temptation I may eat almost against my will can t say why

Treatment of obesity by psychiatric methods

Shorvon and Richardson report losses of weight of up to 2 stone in their patients after treatment by abreaction They found that it was not necessary for the patient to re experience the original disturbing incident and that abreaction of its If could be beneficial if the emotional release were of sufficient intensity

The function of psychotherapy in the obese patient is to promote the formation of new attitudes which enable the individual to find self fulfilment in living so that he does not need to dep nd on primitive oral satisfactions

A woman aged 29 years began to put on weight during pregnancy The man she married was a second choice and the marriage took place during a phase of unhappiness after an affair with another man for whom she still had deep feelings She found very soon after the wedding that her husband was still much attached to his mother and under her domination She had little desire and objected to coitus The husband was himself ill with diabetes was irritable and impulsive and sometim s hit her She was kept in a psychiatric clinic for a month and afterwards remained under supervision as an out patient She separated from her husband and went to work she became interested in her job and enjoyed it When last seen she felt very well and had lost 2½ stone

Ulcerative colitis

Correlation of illness and life situation

During the last 20 years the observation that ulcerative colitis may appear a setting of emotional tension has been made many times over Murray writing in 1930 said What appears in these cases is a well marked time relationship b tween the outbreak of an emotional disturbance and the onset of symptoms Of 7 men studied by him all except 1 were tied to their mothers none was married and for the most part the onset of colitis was associated with a conflict between the mother tie and the desire for marriage Sullivan (1935) pointed out that the latent period between emotional upheaval and appearance of bloody diarrhoea may be short in 11 of his 15 cases this interval was less than 48 hours The relation between a precipitating event and the start of an attack can the more easily be shown according to Daniels (1942) since the bodily response is so prompt

As in other adaptive disorders the precipitating event may not appear in its true colours until the patient s personality and reaction patterns are clearly understood

that anxiety may produce this effect by interference with water balance and cites as evidence for his hypothesis the experiments by Verney on dogs subjected to emotional shock and the loss of weight in obese patients which results from a dehydrating regime even when ample calories are supplied I conclude he says that the fat person is one whose adipose tissue is over hydrated rather than over fatted

From my own experience I believe that anxiety is associated with weight gain in certain people whether directly through over eating or through a central influence upon homoeostasis In children the onset may be quite sharply defined as in the case of Peter or less often it may be gradual without any outstanding single event as precipitant Obesity in either parent is uncommon The patient is often an only child

Personality of the obese patient

Bruch (1940 1941 1942) who has made an extensive study of the subject came to the conclusion that simple obesity in childhood is the outcome of mal adaptation of the mother as much as of the child She found that obesity was more common in immigrants than in indigenous families Only in a few families was the marital relationship satisfactory Many of the mothers tried to create for their children a life of abundance and idleness of which they themselves had felt deprived Those who felt insecure and unhappy employed the child for the fulfilment of their own emotional needs and restrained the child s physical activity because of morbid fears that he might come to harm Of the children in Bruch s series half were unwanted and unplanned In most cases the mother s attitude was a blend of over solicitude—over loading the child with concrete signs of devotion and over feeding—and impatient rejection shown by un reasonable and cruel discipline The former was plainly a manifestation of guilt Excessive intake of food and avoidance of muscular activity were found in the majority of children Only one fifth had any individual interests and most of them divided their time between the cinema the radio and the comic strip Most of the children were very slow to achieve a healthy state of independence nocturnal enuresis had persisted in half of them The events which most commonly preceded the onset of obesity were entry into school which was a threat to the child s security and an illness such as tonsillitis

Although I feel sure that maternal attitudes of the type described by Bruch are of considerable importance in the initiation of obesity in children those I have seen have not been as dependent on their parents or as apprehensive of physical exertion as her patients seemed to be indeed many of them were happy and active children who had no important nervous symptoms I am inclined to think that emotional deprivation or spoiling acting over a certain period of time may set the child s metabolism so to speak at a different level so that the body thenceforth takes in more food than it needs The parents of these children who often feel for various reasons some guilt about their management of the child are reluctant to withhold anything that is asked for and tend to accede to the child s demands for food The disorder is thus more on the mother s side than on the child s

Wittkower that there is considerable variation in personality type in colitis patients Passivity and a morbid attachment to one parent which is often ambivalent seem to be salient features of personality

Psychotherapy of ulcerative colitis

Reports on the effectiveness of psychotherapy have been few Sullivan said of his series of cases that psychotherapy produced striking results when many other forms of therapy had failed Psychotherapy was successful in 4 of Groen s 6 cases he described his treatment as emotional catharsis and encouragement Paulley considers that psychotherapy is likely to do most good in young men and least in middle aged single women

Grace (1950) reported the results of psychiatric treatment of 20 patients with ulcerative colitis ranging from those with mild symptoms to those with an illness so severe that operation was considered The average duration of illness before treatment was 6 years Treatment was by interview at weekly or monthly intervals the patient was given strong support sympathy and reassurance and opportunity to express freely his feelings and conflicts After 15 months of treatment 3 of the patients were symptom free 10 were much better 5 were unchanged and 2 worse

Maine and I (1949) reported the successful treatment of a girl of 19 years We found that the first marked change in her physical condition coincided with an alteration in her attitude and behaviour, in that she became more self assertive and aggressive and more outspoken in her criticisms of the clinic staff and of her own relatives in short the release of pent up aggressive impulses seemed to be the mental correlate of recession in the physical symptoms

DIAGNOSIS AND TREATMENT

To find if a reaction to stress is manifesting itself through gastro intestinal dis order we must seek to learn if the disorder appeared at a moment of crisis major or minor in the patient s life and if its course can be related to the tides of the patient s emotional life We have to know something of the patient as a person his hopes desires and fears his loves and hates his ambitions and his daydreams the tenor of his life We try to find where his heart is the heart of one man is in his work that of another in his home his hobbies or his lust for power It is there in his feelings and strivings that the source of tension lies His life story will tell us these things if we have the time and patience to listen Time and patience are the great limiting factors in the biographic study of illness but it is surely a good investment to learn something of the inwardness of illness right at the start that will save time in the long run

What the patient can tell us about the bearing of emotional states on his symptoms is a function of his insight Even intelligent and thoughtful people can be quite unaware that their symptoms have a meaning There is something in all of us which opposes the recognition of stress symptoms for what they are something which wants to preserve the *status quo* and resists the effort to change it If their resistance is not too high most patients quickly come to see how their bodily state is influenced by feeling When they cannot allow themselves this

A man aged 44 years with ulcerative colitis was admitted for investigation There had been two severe attacks one in 1938 and one in 1948 The patient was at first inclined to deny that there had been anything in his life to disturb him at these times He was single and lived with his mother He did his work without complaint but was dissatisfied with his life and felt he should have made more of it He said that he would like to marry but he was not attracted to women and could not talk to them At the third interview he said that in the summer of 1938 a lad of 18 stayed in the house and shared his bed He admitted that he experienced sexual excitement on this occasion and had an ejaculation After this he slept poorly for 3 weeks and the diarrhoea began He recognized that being touched by a boy caused him to have an erection but he disapproved strongly of any sexual relationship between men In 1948 he went to a holiday camp with a boy of 10 and stayed in the same cubicle with him Again there was strong sex feeling aroused an unsuccessful attempt to suppress it and a good deal of anxiety Dream analysis showed that the patient s libidinal impulses were directed entirely towards his own sex and that he had no erotic interest in wom n at all In time he came to accept this situation without shame He was kept under ob servation and so far has not had a recurrence of colitis

Personality patterns in colitis patients

Sullivan (1935) commented that most of his patients were neat and fussy all but 2 of the group of 15 had some sexual mal adjustment and 5 of his male patients had an abnormal attachment to the mother From a study of 6 patients Groen (1947) concluded that there were certain character traits common to all His patients showed a well defined and often exaggerated carefulness and neat ness they were very sensitive to criticism and had inferiority feelings They were self centred and passive in their attitude to life and they had a great need for sympathy and affection though they gave little sympathy themselves All the men had a strong fixation on the mother Paulley (1950) reported the results of a survey of 173 cases He found that colitis patients were excessively dependent and under the control of the parents usually the mother They were never out wardly aggressive though often querulous The men were rather effeminate As a group the patients were inclined to self righteousness smugness and false modesty they were emotionally immature He compared the colitis patients with a control group taken from a department of radiotherapy only 5 of these had a personality pattern close to that outlined above though 30 per cent showed some traits of emotional immaturity

Wittkower (1938) in his well known paper did not find any such uniformity in the patients he examined He divided them into three main groups In the first the outstanding characteristics were over conscientiousness over scrupulous ness orderliness cleanliness and obstinacy the features of an obsessional per sonality The second group was made up entirely of women who were impulsive moody and excitable they tended to dramatize their lives and had many male admirers but were incapable of giving love This group could be classed as hysterical The third group less well demarcated than the others was distinguished in the main by social anxiety

From my own experience I believe that ulcerative colitis often occurs as a reaction to stress that is it appears at a time of emotional crisis in the patient s life and its recurrences can be correlated with critical situations I agree with

pendence on the physician yet this may be all that is possible Whatever can be done to make external circumstances easier for the patient is worth doing When a husband is ill it is always useful to see the wife and *vice versa* Relations between them often get better when this is done though it may be difficult to see why it is as though some tension is relieved Inter personal relations—bitter, jealous or hostile feelings of one person for another—these are the root of much of the bodily disorder with which we have to deal and what help we can offer, however little is worth while

REFERENCES

Ahronheim J (1947) *Psychosom Med* 9 51
Berk J and Frediani A (1944) *Gastroenterology* 3 435
Bruch Hilde (1940) *Amer J Dis Child* 59 739
— (1940) *Ibid* 60 108?
— (1940) *Psychosom Med* 2 141
— (1941) *Amer J Orth psychiat* 11 467
— (194) *Amer J Psychiat* 99 752
Craig J (1948) *Brit Med J* 2 330
Crider R and Walker S (1948) *Arch Surg* 57 1
Cunha F (1948) *Amer J Surg* 76 244
Cushing H (193?) *Surg Gynec Obstet* 55 1
Daniels C (1942) *New Engl J Med* 226 178
Davies D and Wilson A (1937) *Lancet* 2 1353
Dodds E, (1950) *Proc R Soc Med* 53 34
Doll R and Avery Jones F (1951) *Medical Research Council Spec Rep Series No* 276
Dubois I (1940) *J Psychol Neurol Lp* 106 107
Duncan C Stevenson I and Ripley H (1950) *Psychosom Med* 12 23
Edwards H and Copeman W (1943) *Brit Med J* 2 640
Gill A M (1947) *Lancet* 1 291
Gilsenan B (1946) *Practitioner* 156 456
Glatzel H (1949) *Ar t Woch* 4 165
Grace W (1950) *Psychosom Med* 12 395
Graham S (1951) Personal communication
Greene R (1950) *Proc R Soc Med* 63 344
Groen J (1947) *Psychosom Med* 9 151
Hamilton M (1950) *Brit J Med Psychol* 23 182
Halliday J (1948) *Spec Rep Ser med Res Coun Lond* 276
Halstead J (1946) *New Engl J Med* 235 747
Kaldegg A and O Neill D (1950) *J ment Sci* 96 190
Kapp I Rosenbaum M and Romano J (1947) *Amer J Psychiat* 103 700
Kirk R (1946) *Gastroenterology* 7 168
McCullagh E and Tupper W (1940) *Ann intern Med* 14 817
MacKeith R and O Neill D (1951) *Lancet* In press
Maine J and O Neill D (1949) *Guy s Hosp Rep* 98 113
Maingot R (1949) *Post Grad med J* 25 197
Marcussen R and Wolff H (1949) *Psychosom Med* 11 251
Mittelmann B and Wolff H (1942) *Ibid* 4 5
— — (1943) *Ibid* 5 ?11
Murray C (1930) *Amer J med Sci* 180 239
O Neill D (1950) *Post Grad med J* 26 64
Paulley J (1950) *Gastroenterology* 16 566
Rahman L Richardson H and Ripley H (1939) *Psychosom Med* 1 335
Ripley H and Wolff H (1950) *Psychosom Med* 12 215
Rose J (1943) *Ibid* 5 117
Ross C (1938) *Lancet* 1 1041

recognition or when they notice and then hotly deny it the prospect for causal therapy is bleak and if the physician tries to press on with it they stop coming to him Such patients are the exception As a rule the links of stress to symptom can be made clear within a few interviews The life chart is a useful device for this purpose Symptoms are written in one column events and the patient s reaction to them in another and the patient as he draws it up can see how they tally The latent period between stress and symptom varies in abdominal pain it is short and in duodenal ulcer it may be as long as several days

Naturally we do not expect the patient to tell us what place the illness occupies in his psychic economy that he is using it for example to extort compensation from his firm or attention from an unsympathetic wife This we must judge for ourselves and it is helpful to know what the firm or the wife have to say on the matter Having an illness in some middle aged ladies is an occupation which takes the place of a true purpose in life and it is unwise and unkind to attempt a cure Other and subtler meanings of every kind and shade and degree belong to the illnesses we see and treat from day to day and we can help the patient if we know them

When a child is ill we do well to remember that mother and child are an organic unity it is vain to deal with one without the other It is a good use of time to spend the first session or the first two with the mother alone to find her story of the illness something of her own life and of the nexus of feeling which binds her to the child and the child to her It is not rare for the child to improve after this has been done before he himself has been seen no plainer proof could exist of the reciprocal influence of the one on the other There is no difficulty about setting up rapport with a child some become anxious when the mother goes to sit outside as she should but this will pass as they get used to the situation if there is something in the room worth staying for It is not reasonable to suppose that a young child will tell us in words what the trouble is about he has not the words for that and we must employ another medium such as drawing or painting or a set of puppets to represent his family and friends upon which he can project his conflicts and fantasies In my experience stress disorders in childhood are satisfactory material for the therapist if they are going to respond at all they do so quite soon

To see the patient once a week for half an hour or an hour is to give as much time as most physicians can afford luckily the disorders we have been considering do improve on this dose of therapy If the interval is much longer interest flags and the oppositional forces in the patient rise up anew and defeat us Resistance to therapy is the patient s main enemy and ours It may show itself as hostile and critical comments on ourselves and our treatment and we have to be ready for this and soak it up without being affronted For some patients only skilled and intensive psychiatric treatment is of any use we become aware of this by the depth of disturbance which comes to view when we explore the background of illness and it is wise to refer them early to a special centre for psychotherapy

The aim of treatment is to make the patient independent of ourselves of drugs and of emotional demands on others This is an ideal aim and it is seldom attained Removal of symptoms is of less value if the illness is merely exchanged for de

CHAPTER 4

ABDOMINAL PAIN

G W PICKERING

ABDOMINAL pain is one of the most frequent and sometimes the most baffling of symptoms with which the doctor is called upon to deal Thus it may arise from a large variety of tissues and organs which are mostly relatively inaccessible to investigation Moreover there is still a very considerable gap in our knowledge of the mechanism by which pain arises from many of the tissues in question Finally as is usual where knowledge is deficient hypothesis has flourished like a weed and has become incorporated in medical teaching in the guise of so-called principles to befog the outlook of many past and present students of this question This article cannot attempt a full historical account of these hypotheses and the work on which they are based but the hypotheses have arisen because of the so-called reference of deep pain and because of the relative insensibility of the gut From a practical point of view one of the most important problems to become so confused is that of somatic and visceral pain

PAIN OF SOMATIC AND VISCERAL ORIGIN

From the day he begins his professional studies the student is encouraged to think of the abdomen in terms of viscera In anatomy the comparative simplicity of the abdominal wall with its familiar muscle tendon and fascia contrasts with the unique and complex collection of organs which it contains In surgery the importance of the acute abdomen the difficulty in diagnosing which of the various catastrophes may have occurred and the life saving effect of the appropriate operative intervention again focus attention on the viscera Newly qualified doctors and indeed many of maturer years at once think of visceral disease when a patient presents himself with abdominal pain Unfortunately many of the sensory and motor phenomena associated with visceral disease are indistinguishable from those occurring with lesions of the deep somatic structures and so it may happen that the unfortunate patient whose lesion is not visceral but is somatic is subjected to a series of laparotomies by a succession of enthusiastic specialists whose vision is focused on the organ of his choice Since women have more spare time for these exercises and a greater variety of non essential intra abdominal organs the classical picture of the much scarred abdomen and the unrelieved pain is presented by the so called abdominal woman To prevent this iatrogenic disease the doctor must have a clear conception of the characteristics of somatic and visceral pain

Quality

Lewis and Hess (1933) and Lewis (1938) showed that the subject can distinguish only two qualities of pain that arising from the skin and that arising from structures

Ryle J (1936) *Lancet* **2** 893
Schindler R (1927) *Die Psychoneurosen des Verdauungstrakts* Leipzig Hirzel
Shorvon H and Richardson J (1949) *Brit med J* **2** 951
Stevenson I Duncan C Wolf S Ripley H and Wolff H (1949) *Psychosom Med* **11** 257
Sullivan A (1935) *Amer J Dig Dis* **2** 651
Tidy H (1943) *Brit Med J* **2** 473
Weiss E (1944) *Psychosom Med* **6** 58
Wittkower E (1938) *Brit Med J* **2** 1356
Wolf S and Wolff H (1943) *Human Gastric Function* New York Oxford University Press
Wolff H (1947) *Ann intern Med* **27** 944

Pain arising from stimulation of the ninth thoracic inter spinous ligament occurs in an area behind over the angle of the scapula and in an area over and below the right costal margin This distribution is very similar to that often seen in gall bladder disease Pain arising from stimulation of the first lumbar inter spinous ligament is felt in the back just above the iliac crest in the iliac fossa in the groin and in the testicle It corresponds exactly to that of renal colic The second point to be made therefore is that pain arising from a deep somatic source may have precisely the same area of distribution as that arising from visceral disease That in these two instances pain may be referred to an area of the body image that does not correspond with its actual source means of course a faulty localization by the brain The brain possesses a remarkable ability to localize stimuli arising from the skin and to a less extent from the immediately subjacent structures Whether this is inherent or is learned by experience is not known though the latter would seem the more probable In the case of the deeper structures this ability to localize is lacking and indeed it is difficult to see how the brain would have any opportunity of learning to localize in the case of these structures that are inaccessible to eyes or fingers no doubt the actual reference of pain is determined by the path of the sensory impulses in the brain

Tenderness and rigidity

Lewis and Kellgren (1939) have shown that when deep somatic structures are stimulated an area of deep tenderness is produced corresponding closely to the area of pain The muscles of the body wall are also thrown into a sustained contraction Thus stimulation of the right first lumbar inter spinous ligament produces deep tenderness of the erector spinae muscles and those of the anterior abdominal wall in the right iliac fossa and tenderness of the testis At the same time there is a sustained contraction of the muscles named and retraction of the testicle These phenomena are of course well recognized as characteristic accompaniments of renal colic Thus the third point is that the deep tenderness and muscular contraction arising from stimulation of a deep somatic structure may be indistinguishable from those of a visceral lesion

Differentiation of somatic and visceral pain

Disease of the abdominal viscera produces pain which is of the quality of deep pain in general Its distribution is often rather characteristic of the visceral lesion concerned as are the associated tenderness and rigidity Nevertheless the diagnosis of a visceral as opposed to a deep somatic lesion cannot be made on these criteria alone for all are common to both The diagnosis is made on the factors that precipitate and relieve pain the time relations of the pain and the presence of other phenomena indicating a visceral lesion Deep somatic lesions are often the result of minor trauma to muscle ligament or tendon and tend to have a sudden onset during muscular activity The pain is usually continuous and may last days weeks or even years without much intermission which is rarely true of visceral pain The patient is rarely ill with a deep somatic lesion fever leucocytosis and a raised erythrocyte sedimentation rate are uncommon Sometimes the somatic lesion gives a characteristic radiographic appearance as for example with prolapse of an intervertebral disc In skilled hands the somatic source

deep to the skin Thus if care is taken to exclude associated sensations then a variety of stimuli applied to the skin such as a burn a freeze a pinch a hair pull a prick will all be recognized as a prick if the stimuli are brief and as a burn if the stimuli last long If the skin is anaesthetized any deep somatic structure can be stimulated by passing a needle through the anaesthetic skin down to the structure in question and scratching it with the needle point or injecting 6 per cent saline into it The subject will recognize the pain so produced as different from skin pain it is a dull ache as contrasted with sharp pain from skin He will not be able to say whether the tissue stimulated is tendon muscle fascia ligament periosteum artery or vein Moreover if in a subject who has experienced pain of visceral disease pain is produced from a deep somatic structure such that the distribution of pain is the same as that of the visceral disease then the subject is unable to distinguish between the qualities of the pain The first point to be made therefore is that the quality of the pain arising from visceral disease is identical with that of pain arising from a deep somatic source It follows that in the differential diagnosis of abdominal pain little help is to be obtained from the patient s description of the quality Quality of pain is often described in terms of experience the patient recognizing the similarity of pain associated with an earlier event but very often the term the patient uses is of imagined experience Abdominal pain is often described as gnawing and some patients will go further and identify the species of rodent concerned The author has yet to meet a patient who has actually had the experience of being gnawed and feels that such epithets give no useful information as to the pain though they are of course an interesting feature of the patient s mind

Localization

Pain arising from a stimulus applied to the skin is accurately localized to the point stimulated Pain in visceral disease is often felt over quite a wide area of the body image and is not infrequently localized to a point distinct from the actual position of the viscus To account for this difference there has been a spate of hypotheses that need not be reviewed here One of the earliest to which Kinsella (1948) has drawn attention was that of John Hunter who supposed that the sensation of pain coming from a part different from its actual origin might be due to communications between the nerves serving the two or to their connections in the brain This is very much like the modern hypothesis arising from the work of Kellgren (1939) and Lewis and Kellgren (1939) which will now be described

Kellgren (1939) has shown that if a somatic structure lying under the skin is stimulated then the pain is localized to an area close to the stimulus if the point stimulated is superficial but may be felt at a distance if the point stimulated is deep Thus stimulation of periosteum on the spine of the scapula or tip of vertebral spine gives pain closely adjacent to the stimulus but stimulation of periosteum in the intra spinous fossa or on the body of the vertebra gives pain of wider distribution and some distance away Kellgren has shown that the reference of pain arising from deep somatic structures follows roughly a segmental pattern In the thoracic and abdominal regions pain is felt usually over an area in front and an area behind the flanks being free from pain Two examples may be given

posterior wall ulcers it frequently involves also the back and it may occur in quite different sites which will be mentioned later The pain usually begins gradually at some more or less well defined time after a meal and increases to a maximum at which it remains until it is relieved by food by vomiting or alkali or if by none of these until it gradually passes off It is generally believed that in duodenal ulcer the pain tends to begin later after meals than in gastric ulcer and that it occurs more frequently at night As a generalization this is probably correct but exceptions are not infrequent It is also generally true that a history of relief of pain by food is much more common in duodenal ulcer and this because the patient with gastric ulcer does not usually eat with his pain either because he has recently eaten and is not hungry or because he is nauseated

The older teaching as to the mechanism of pain in ulcer ascribed pain to tension in the walls of the stomach and duodenum This teaching arose from the conception already mentioned that the pain nerves of the stomach and duodenum would only respond to such a stimulus and from experiments of Hurst (1911) in which he failed to produce pain by injecting dilute hydrochloric acid into the stomach of patients with peptic ulcer When the hypothesis attempts to explain the relief of pain from introduction into the stomach of such different volumes and kinds of substances as a large meal and a teaspoonful of alkali and the relief of pain by removing the stomach contents by vomiting or aspiration it becomes very laboured and the arguments rather specious In fact the well known characteristics of pain that can be elicited from the clinical history suggest strongly a very different mechanism The relief of pain by food by alkali and by vomiting suggests that the pain is due to the stimulus of intra gastric acidity for the only factor common to the three agents mentioned is that they remove hydrogen ions from the stomach This hypothesis received support from Palmer (1926 1927 1934 1940 1943) and others who showed in 1926 that the injection of 200 milli litres 0 5 per cent hydrochloric acid into the stomach would reproduce the pain in most patients with gastric duodenal and anastomotic ulcer and in many patients with gastric cancer during the period they were experiencing spontaneous pain but not usually in the same patient when as a result of treatment pain had ceased to occur naturally He showed that pain of ulcer could be relieved by aspirating and reproduced by re injecting the gastric content through a tube lying in the stomach He found close agreement between the titratable acidity of the gastric content removed during spontaneous pain and that produced by injection of acid He concluded that hydrochloric acid was the irritant common to all the solutions which constituted an adequate stimulus to the pain producing mechanism and that since pain could also be produced by sulphuric and acetic acids and by caustic soda hydrochloric acid probably acted as a chemical irritant He could find no convincing evidence from balloon experiments and radiological investigation after giving acid barium sulphate that pain was always or usually associated with gastric contraction

Though others (Hardy 1929) obtained results which confirmed those of Palmer there were certain observations not in agreement with the acid hypothesis such as the failure of several workers to find consistently greater acidity in specimens removed from the stomach in the presence of pain than during its absence (Christensen 1931 Hardt 1918) Moreover the presence of proved peptic ulcer

can often be found by deep palpation and exploration with a needle from the point of which pain resembling that felt naturally is elicited injection of Novocain into the lesion will sometimes abolish the pain permanently

The relative insensibility of the gut and other hollow viscera

Lennander (1902 1906) *Wilms (1906) Mackenzie (1909) and others (Breslauer* 1921 Kappis 1921) operating after local anaesthetization of the anterior abdominal wall and usually after injection of morphine have agreed that the hollow viscera of the abdomen are absolutely or relatively insensitive to stimuli which in skin and other structures produce pain Thus the gut from the cardiac opening of the diaphragm to the beginning of the anal canal can be cut burned or crushed without the subject feeling pain but if the mesentery of the stomach small or large intestine be pulled the subject at once complains of pain which is usually felt over a wide area centrally in the abdomen above and below the umbilicus These observations have led to a number of hypotheses that attempt to account for the pain of visceral disease Lennander (1902) supposed that the pain arose from the posterior abdominal wall where and only where he had been able to demonstrate sensibility to pain He supposed that in peptic ulcer pain substances were transported from the ulcer through the lymphatics of the mesentery to diffuse out and around the nerve endings In colic he supposed that the powerful contractions of the gut put tension on its mesentery and so *produced pain mechanically* Nothnagel (1905) *observing pain during contraction* of the bladder and gut in vesical and intestinal obstruction put forward the notion that the hollow viscera were in fact endowed with pain nerves which do not respond to ordinary stimuli but only to an adequate stimulus in this case anaemia For Hurst and Stewart (1911 1929) the adequate stimulus was tension for Kinsella (1948) compression of the nerve fibres The behaviour of the gut nerves in this respect is held to resemble the retina the nerve endings of which respond only to the stimulus of light As Lewis (1942) has pointed out the analogy is false for all nerves respond to mechanical stimulation and while section of the optic nerve gives rise to a sensation of a flash of light section of gut gives no sensation whatsoever

A *very similar situation arises in the case of the heart which has never been* shown to be sensitive at operation under local anaesthesia (Alexander Macleod and Barker 1929) Yet here there is very convincing evidence that in myocardial infarction and angina pectoris pain does arise from the heart itself

The difficulty in the case of the gut is partly resolved by Kinsella (1948) who has shown by very careful observations that squeezing or pinching the inflamed appendix or the inflamed surroundings of a peptic ulcer gives rise to pain in the patient whose belly has been opened under local anaesthesia It seems probable that there are pain nerve endings in the gut but presumably some kind of temporal or spatial summation of the impulses they transmit to the central nervous system is necessary before pain is felt

PAIN IN PEPTIC ULCER

Ulcer pain is a continuous ache of the deep pain type usually felt over an area about the size of a palm in the mid line of the epigastrium In penetrating

Whatever the point of view from which it is approached the acid hypothesis *seems to be in conformity with the facts Moreover it is not difficult to see how* the circumstances that have led to the rejection of the acid hypothesis arose The failure of Hurst and others to elicit pain by acid in gastric ulcer could have occurred if healing had progressed to the point of making the pain mechanism insensitive for insensitivity is known to precede clinical healing or if the acid had not been left in the stomach long enough Isolated samples of gastric contents may not show higher acidities during the presence of pain than during its absence for there is a notable latent period between rise in acidity and onset of pain and between fall of acidity and end of pain when this is experimentally produced It is only by serial sampling that the full relationship between rise and fall in acidity and onset and relief of pain becomes apparent Finally the objection that pain may occur in patients with ulcer who have achlorhydria to fractional and histamine test meals is met by the observations of Watkinson and James (1951) who showed that when the gastric contents are sampled throughout the twenty four hours by the method of James and Pickering (1949) appreciable degrees of acidity are found in the stomach of such patients

Acid might act as the stimulus to pain by producing contraction of the stomach the pylorus or the duodenal bulb A generalized contraction of the stomach is at once ruled out by the observation that pain produced by intra gastric injection of acid is not accompanied by a rise in intra gastric pressure No evidence was found of a local contraction of stomach pylorus or duodenum when pain was produced by intra gastric injection of barium sulphate emulsion containing N/20 to N/10 hydrochloric acid Reynolds and McClure (1922) producing pain by the ingestion of lean beef mixed with barium sulphate and subsequently inspecting the stomach and duodenum by radiological examination came to a similar conclusion Kinsella (1948) is impressed by the slow emptying of the stomach when acid is administered an observation also made by Bonney and Pickering he attributes this to pyloro spasm The slow emptying is however in large part due to the quiescence of the stomach and is equally notable in normal subjects who experience no pain It would seem therefore that acid acts as a chemical irritant in producing pain

Thus far the observations of Bonney and Pickering in the main confirmed those earlier obtained by Palmer An attempt was then made to locate the nerve endings Kinsella (1929) Hurst and Stewart (1929) and Morley and Twining (1931) observed that tenderness elicited by deep palpation of the anterior abdominal wall coincided with the position of the ulcer as seen radiologically Morley and *Twining finding remarkable coincidence in shift of deep tenderness and ulcer* with change of posture * It is very generally assumed that this deep tenderness implies that the ulcer itself is tender though Morley and Twining adopted a different interpretation Now if the ulcer itself is tender it must contain pain nerve endings To verify this conclusion regional anaesthetization of the anterior abdominal wall was produced by blocking the intercostal nerves from Th 4 to Th 11 on both sides In patients who developed good anaesthesia tenderness previously present on palpation disappeared The simplest explanation of this

* The [illegible] ha[illegible] ev[illegible] be[illegible] [illegible] mak[illegible] [illegible] ny defi[illegible] shift in deep tenderness with [illegible] nge of po ture in pep[illegible] [illegible]

in patients showing achlorhydria to the fractional test meal and even to histamine has convinced many (Ryle 1926) that the acid hypothesis must be wrong

In view of the conflict of evidence the writer in 1940 began observations designed to test the two hypotheses of peptic ulcer pain and these were completed with Bonney (1946a and b) These observations in the main confirmed those of Palmer It was found that in patients with ulcer pain aspirating the gastric contents would relieve the pain during the aspiration Returning the gastric content usually brought back the pain after a latency of several minutes but not if the gastric contents were first neutralized Again in most patients with gastric duodenal and anastomotic ulcer and in the few cases of gastric cancer tested injection of 200–300 millilitres of N/20 to N/10 hydrochloric acid into the stomach would produce pain after a latency of about 10 minutes the pain being relieved by emptying the stomach or by neutralizing the gastric content with alkali This was the case if the patients were tested at a time when they were experiencing ulcer pain naturally but repeating the test with the same patients when the ulcer had healed produced no pain Just as pain arises when dilute hydrochloric acid is applied to the skin when the epithelium is breached by a cut a scratch or a sore but not when the epithelium is intact so it would seem that pain arises from a similar stimulus in the stomach provided that there is a lesion of the mucous membrane though the relative inaccessibility of the stomach prevents us from saying with precision what is the precise characteristic of the lesion which makes it sensitive to acid whether it is simply the presence of a breach in the endothelium or whether it is the presence of an inflammatory reaction As we shall see there are grounds for supposing that the degree of exposure of pain nerve endings may be at least one factor in sensitivity

In view of the latency between the introduction of acid into the stomach and the appearance of pain and between the neutralization of acid and the disappearance of pain averaging 10 and 8 minutes respectively in the case of gastric ulcer it seemed desirable to obtain serial readings of intra gastric acidity when ordinary meals were taken in order to see if naturally occurring pain was related to fluctuations in intra gastric acidity Here a source of error was found for the acidity of samples from cardiac and pyloric ends of the stomach may be widely different though this discrepancy is chiefly pronounced immediately after a meal and the acidities at the two ends of the stomach subsequently approximate Nevertheless it was observed that when the stomach was sampled at half hourly intervals in gastric duodenal and anastomotic ulcer there was a clear relationship between intra gastric acidity and pain Thus pain occurred when the stomach contents become more acid and disappeared when they become less acid pain nearly always occurred in a particular patient when the intra gastric acidity exceeded a certain level for a certain time and it never occurred when gastric acidity was less than a certain value for a given time It was of some interest to observe that the threshold value of acidity above which pain occurred varied a good deal being on the whole highest in duodenal ulcer and lowest in anastomotic ulcer and gastric cancer where it was sometimes not higher than the turning point of Topfer s reagent Finally a reasonably close agreement was found between the levels of acidity provoking pain when acid was injected into the stomach and those at which pain occurred naturally

statement that Bonney and Pickering noted pain even when the gastric juice was persistently alkaline or neutral to litmus is untrue He presents the hypothesis that pain is due to compression of nerve fibres in the ulcer through a coincidence of 3 factors the pathological hyperaemia of the ulcer base the physiological hyperaemia of digestion and the postural contraction or retraction of the wall of the emptying stomach He attributes relief of pain by food to the hyperaemia of digestion which relieves the tension in the ulcer tissue by opening up the neighbouring capillary bed in the healthy stomach wall The relief by alkali is attributed to a relaxation of the pyloric duodenal musculature and to active hyperaemia Vomiting stops pain by relieving the stomach of its duties putting it to rest Unfortunately there is no evidence that pain is ever due to compression of nerve fibres in tissues by the order of tissue pressure that may exist in an inflamed ulcer Nor is there evidence for the mechanisms suggested by Kinsella for the relief of pain In fact Kinsella would reject what evidence there is for he says the relaxing effect of antacids cannot be shown by balloon or kymographic studies in these the base line represents intra abdominal pressure which is not affected by antacids or acids It is of course quite possible to record pressure from within and without the gut Kinsella s point that the degree of inflammation of the ulcer may be of importance in determining its pain sensitivity is a valid one is in line with experience elsewhere in the body and was also suggested by Bonney and Pickering

The full hypothesis of the mechanism of ulcer pain as developed by Palmer and by Bonney and Pickering has several clinical implications The first is that unless perforation has occurred ulcer pain should always be capable of relief by alkali So far as the writer s experience goes this is true Not infrequently patients will state that their pain has recently become refractory to alkali but whenever the writer has given such a patient two drachms of powdered alkali pain has been abolished A more limited experience agrees with that of Palmer and that of Sippy in that ulcer pain can nearly always be relieved by gastric aspiration A second implication of the hypothesis is that pain having the characteristics of peptic ulcer pain particularly in being relieved by alkali is always due to a lesion such as an erosion a benign or malignant ulcer of the mucous membrane of the stomach or the cavity immediately proximal or distal to it This is of course opposed to the traditional teaching that pain resembling ulcer pain may arise reflexly from appendix gall bladder and colon a hypothesis for which only rather tenuous evidence exists The chief difficulty in investigating the truth or otherwise of this idea is the difficulty in being sure whether or not there is a lesion of stomach or adjacent cavity The very high error of radiology in acute ulcer has been shown by Avery Jones (1943) nor is surgical exposure of the stomach always reliable for acute ulcers may not be recognized unless the cavity is opened and the mucous membrane all inspected very carefully Gastroscopy leaves some areas uninspected For these reasons this question remains open

The third implication is that should the structures forming the floor of the crater be unusual then the reference of the pain may also be unusual Examples of this have been cited by Bonney and Pickering of an anastomotic ulcer adherent to the anterior abdominal wall producing pain over the seventh rib and of large posterior wall gastric ulcers producing pain in right or left iliac fossae In all these cases the pain though of unusual site was relieved by food by alkali or by vomiting

observation is that the tenderness in fact lies not in the ulcer but in the anterior abdominal wall an explanation previously advanced on other grounds by Mackenzie (1909) Subsequently Kinsella (1948) has shown that if at operation under local anaesthetization of the anterior abdominal wall the inflamed tissue of a gastric ulcer is squeezed pain is produced A similar observation was made in duodenal ulcer by Dragstedt and Palmer (1931) It would seem therefore *that the ulcer crater must in fact contain pain nerves*

A difficulty in accepting that the pain nerves actually stimulated by acid lie in the ulcer crater is the long latent period that elapses between the introduction of acid into the stomach and the onset of pain and between the neutralization of acid and the disappearance of pain In gastric ulcer the average figures for these latent periods were 10 and 8 minutes respectively In trying to interpret these latent periods it seemed desirable to have some kind of yardstick Ulcers were therefore made on the forearm by shaving off the superficial layers of the epidermis In such preparations the pain nerves lie at the surface of the living tissue If to such ulcers 16 to 20 hours old isotonic hydrochloric acid (0 15N) is applied pain begins within a few seconds and is relieved in a similar period by neutralization The time relations are slightly lengthened if the ulcers are previously coated with a thin layer of mucus If the ulcers are tested at 96 hours by which time the serum exuded has dried to form an adherent scab then pain develops 3 to 6 minutes after applying acid and disappears on neutralization after a similar period Histological examination of a peptic ulcer shows that the living tissue at the base of the ulcer is covered by a slough of necrotic cells and fibrin and this on measurement is about the same thickness as were the scabs in the skin ulcers It would seem therefore that the latent period elapsing between acidification and neutralization of the stomach contents and the onset and end of pain is due to the interposition of an inert membrane between the stomach contents and the pain nerve endings for it takes time for a change in the composition of the fluid on one side of the membrane to produce a given degree of change on the other

These observations thus support very strongly the idea that pain occurs in peptic ulcer when the acidity of the gastric contents rises to a level high enough to stimulate the pain nerve endings situated in the ulcer crater and that acid acts in this respect as a chemical irritant The situation would in fact appear to be very closely analogous to what can be observed on the skin If the surface is intact N/10 acid produces no distinctive sensation if the surface is breached pain occurs The one outstanding difficulty is the apparent insensitivity of the stomach at operation It is worth noting however that a similar dilemma exists in the case of the heart William Harvey showed to Charles II the apparent insensitivity of the heart an observation since confirmed (Alexander MacLeod and Barker 1929) Yet there is convincing evidence that in angina pectoris and myocardial infarction the pain arises from the heart itself

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APPENDICITIS

The dramatic succession of events their swift enactment and the accessibility of the diseased structures to the eye and finger at operation have combined to make appendicitis one of the chief topics for debate between the rival protagonists of all embracing hypotheses of visceral pain The facts are generally known The attack begins with bouts of poorly localized central abdominal pain resembling intestinal colic After some hours this is replaced by a rather sharper and more constant pain in the right iliac fossa During the central pain it is exceptional to find tenderness or rigidity of the anterior abdominal wall During the second pain rigidity and tenderness in the right iliac fossa are the rule with an appendix in the ordinary position but with a pelvic appendix both may be absent and replaced by tenderness elicited from the right wall of the pelvis by rectal examination The first pain has been variously supposed to come from the small intestine the mesoappendix and the appendix itself Kinsella s (1948) observation that in a patient at operation under local anaesthesia pain can actually be elicited from the acutely inflamed appendix when it is squeezed between the fingers makes the appendix which is the primarily diseased organ the most probable source of the pain The second pain must have a different origin and Morley s (1931) contention that the pain and associated phenomena are probably due to spread of the inflammatory process to the posterior or lateral abdominal wall is probably correct Morley s evidence for this view is the very close correlation between the distribution of tenderness and rigidity and the position of the appendix relative to the posterior abdominal wall

Concerning the vexed question of chronic appendicitis the writer feels that the most succinct account is Ogilvie s (1937) advice to his registrars never to admit its existence until they are thirty five and never to take a fee for operating on it until they are forty years old It is rather uncommon to find symptoms which persist without intermission for many weeks and disappear after appendicectomy On the other hand it is common and in fact the rule in some clinics to find that any patient with persistent pain in the right iliac fossa is diagnosed as chronic appendicitis and has an appendicectomy From what was said earlier about visceral and somatic pain the reader will appreciate that such pain may arise from a whole variety of deep somatic structures innervated by segments Th 10 to L 1 Further if pain of deep somatic origin is referred to the right iliac fossa the muscles there will be tender Thus the surgeon palpating the right iliac fossa will elicit tenderness and his suspicion of chronic appendicitis will be confirmed To make quite sure he will send the patient for radiological examination At the appropriate time after the meal the radiologist will see the appendix completely or incompletely filled with barium lying in the right iliac fossa Palpating the appendix with his leaded fingers he will of course elicit pain from the tender muscles Since muscles are relatively invisible in radiographic examination their existence is overlooked and the radiologist concludes that it is the appendix that is tender So he confirms the diagnosis Where such an attitude persists a patient with right iliac pain of deep somatic origin is automatically subjected to appendicectomy Not infrequently the pain persists and there are unfortunately some patients whose appetite for surgery is whetted by their experience and who embark on a career of miscellaneous and unsuccessful abdominal operations

THE PAIN OF GASTRIC CANCER

As has already been mentioned pain in gastric cancer may have the same characteristics as elicited in the history and may behave in the same way to experimental interference as does the pain of peptic ulcer and in these cases it may be presumed to arise in the same way by stimulation of pain nerve endings in the crater through the irritant action of gastric acid In such cases there is however one clear cut clinical difference namely that just as peptic ulcer is characterized by remissions and relapses while gastric cancer pursues a relentless course so pain due to peptic ulcer tends to come in bouts of weeks or months with intervals of weeks months or years of complete freedom while pain in gastric cancer tends to occur daily and to become progressively more severe unless the patient adopts a regime which maintains a low level of gastric acidity

In other cases of gastric cancer pain may not have these same characteristics and its mechanism is not fully understood

INTESTINAL PAIN

Intestinal colic is a well known and easily recognized pain Usually it has a fairly wide and rather ill defined distribution typically above the umbilicus from small intestine and below the umbilicus from large intestine Its striking characteristic is its time relationship It occurs in bouts pain beginning gently gradually increasing to a climax and then passing away the whole episode lasting about one minute The intervals between these bouts may be a few or several minutes Thanks particularly to Mackenzie (1909) and Nothnagel (1905) it is known that these bouts of pain are associated with waves of intense contraction in the gut Three hypotheses have been produced for the mechanism of this pain that it is due to anaemia of the gut (Nothnagel 1905) that it arises from tension in the wall of the gut (Hurst 1911) and that it does not arise from the gut at all but is due to tension on the mesentery (Lennander 1902, 1906) This particular kind of pain can be produced experimentally by passing a balloon to the appropriate part of the gut and then inflating it So little has been learned of actual mechanism from such studies that there seems no point in discussing this further as any discussion must be almost wholly speculative

Intestinal colic is within the experience of most healthy people and has been due in them to a gastro intestinal infection an unsuitable ingredient of food or a purgative such as senna it is usually associated with or followed by diarrhoea In this respect it contrasts with that of intestinal obstruction due to new growths strangulated hernia and other lesions where the pain is usually more intense and constipation is the rule Recurrent bouts of intestinal colic with or without diarrhoea or constipation may be the first sign of a grave intestinal lesion which requires surgical intervention

The characteristics of intestinal colic are its time relations and its distribution Pain without this striking periodicity is sometimes found in a variety of intestinal lesions and is then often localized to one or other side It is tempting to suppose that in such lesions pain is due to stimulation of nerve endings in the abdominal wall especially the posterior abdominal wall

ureter and the pelvic organs notably in women may cause abdominal pain Inflammation of the peritoneum causes the most dramatic episodes which are dealt with fully in current surgical treatises on the acute abdomen

REFERENCES

Alexand r J MacLeod A G and Barker P S (1929) *Arch Surg* 19 1470
Avery Jones F (1943) *B it me l J* 1 689
Bonney G L W and Pickering G W (1946a) *Clin Sci* 6 63
— — (1946b) *Ibid* 6 91
Breslauer F (1921) *B itr klin Chir* 121 301
Chapman W P Herrera R and Jones C M (1949) *Su g Gynec Obstet* 89 573
Christensen O (1931) *Acta Med scand Suppl* 37 p 1
Dragstedt L R and Palmer W L (1932) *Proc Soc exp Biol N Y* 29 753
Hardt L L J (1918) *J Amer med Ass* 70 837
Hardy T L (1929) *Lancet* 1 711
Hurst A F (1911) *The Sensibility of the Alimentary Canal* London Frowd and Hodder and Stoughton
— and Stewart M J (19 9) *Gastric and Duo l nal Ulcer* London Oxford University Press
James A H and Pickering G W (1949) *Clin Sci* 8 181
Jones C M (1938) *Digestive Tract Pain Diagnosis and Treatment* New York MacMillan
Kappis M (1921) *Arch klin Chir* 121 186
Kellgren J H (1939) *Clin Sci* 4 36
Kinsella V J (1929) *Lancet* 1 1130
— (1948) *The Mechanism of Abdominal Pain* Sydney Australasian Medical Publishing Co
Lennander K G (190) *Mitt Grenzgeb Med Chir* 10 38
— (1906) *Ibid* 16 24
Lewis T (1938) *Brit med J* 1 321
— (1942) *Pain* New York MacMillan
— and Hess W (1933) *Clin Sci* 1 39
— and Kellgren J H (1939) *Ibid* 4 47
Mackenzie J (1909) *Symptoms and their Interpretation* London Shaw
Morley J (1931) *Abdominal Pain* Edinburgh Livingstone
— and Twining E W (1931) *Brit J Surg* 18 376
Nothnagel H (1905) *VerdauKr* 11 117
Ogilvie W H (1937) *Brit med J* 1 1
Ortmayer M (1925) *Arch intern Med* 35 423
Palmer W L (1926) *Ibid* 38 694
— (1927) *Ibid* 39 109
— (1943) Pain *Res Publ Ass nerv ment Dis* 23 302
— and Heinz T E (1934) *Arch intern Med* 53 269
— and Nutter P B (1940) *Ibid* 65 499
Poulton E P (1928) *Lancet* 2 1223
Reynolds L and McClure C W (1922) *A ch intern Med* 29 1
Ryle J A (1926) *Gastric Function in Health and Disease* London Oxford University Press
Watkinson G and James A H (1951) *Clin Sci* 10 255
Wilms M (1906) *Mitt Gren geb Med Chi* 16 609

GALL BLADDER PAIN

In gall bladder disease whether the attacks be due to inflammation of the gall bladder or to impaction of stone in the cystic duct it is the rule to find pain of a fairly well defined character The pain is most commonly epigastric and may radiate through or round one or both costal margins to the back much more commonly the right than the left Pain between the shoulder blades is common and over the shoulder tip rather uncommon The attacks of pain may last minutes commonly last hours and may last a few days Cutaneous hyperalgesia may occur over the right costal margin during the attack and when the gall bladder is inflamed there is pain in the right hypochondrium increased by respiration and pronounced tenderness and rigidity of the right upper abdominal quadrant Lennander found the gall bladder and cystic duct like other hollow abdominal viscera to be insensitive and attributed the pain of gall bladder colic to irritability of the retroperitoneal nerves provoked by infective lymphangitis and to tension on these nerves through stretching the common duct Several observers (Chapman Herrera and Jones 1949 Jones 1938) have shown that in patients who have recovered from operation and have a drainage tube appropriately sited inflating a balloon in the common duct or irrigating it with saline under pressure will produce pain characteristically epigastric or right hypochondriac with radiation to the back though there has been little information about associated tenderness and rigidity The idea that epigastric pain or discomfort in gall bladder disease arises reflexly from the stomach is thus quite without foundation and is an example of the incurable tendency of doctors to invent reflexes and toxins to explain anything not apparent to the more superficial forms of thought It is worth noting in passing that there is a good deal of evidence that pain arising naturally and by experimental induction from a variety of thoracic and abdominal structures is relieved or prevented by anaesthetizing the skin in the distribution of pain (Morley 1931) This observation is interpreted as evidence of Mackenzie s (1909) viscero sensory reflex which is in turn based on the findings at operation under local anaesthesia It is clear that there is an interesting and possibly very important point at issue here which in the writer s view badly needs investigating by one whose mind is not dominated by a hypothesis

There is some evidence that some of the phenomena of acute cholecystitis may arise from the spread of inflammation to the anterior abdominal wall One may cite for example pain on deep breathing which may be associated with a rub and Morley s (1931) curious observation that in acute obstructive cholecystitis the tenderness and rigidity in the right hypochondrium may be observed to extend down the anterior abdominal wall as the gall bladder enlarges

OTHER CAUSES OF ABDOMINAL PAIN

A complete account of all the causes of abdominal pain is beyond the scope of this volume The reader is reminded that the innervation of the diaphragm would seem to account for lesions impinging on it from below or above causing pain in the shoulder tip as well as the hypochondrium and back Lesions in the chest may cause pain in the upper abdomen Lesions of liver pancreas kidneys and

Skiagrams

Stereoscopic skiagrams should be carried out in all parotid diseases when there is any evidence of acute recurrent or chronic pyogenic infection or symptoms or signs suggestive of a calculus and also in all obscure conditions The detection of calculi may be difficult owing to their small size and the presence of the bony shadows Intra oral and extra oral films must be taken in all submaxillary conditions owing to the frequency of calculi Even with great care small calculi may be overlooked

Sialograms

Sialography is the investigation of the ducts of the salivary glands by means of the injection of radio opaque oil Lipiodol can be used for this purpose but the less viscid oils are preferable The method will demonstrate dilatations irregularities or obstructions in the duct system or localize a calculus or fistula Submaxillary *sialography is rarely indicated and is technically much more difficult*

Biopsy

Biopsy has practically no place in investigation First there are few diseases in which the method is likely to be necessary and secondly the risks of a salivary fistula cannot be overlooked

CONGENITAL ABNORMALITIES AND MALFORMATIONS

All congenital abnormalities are extremely rare

Absence or malformation

Congenital absence of one or more of the salivary glands is a very rare condition except in association with extensive malformation of the face Occasionally migration of the parotid may be imperfect and the gland may be situated over the anterior part of the masseter muscle or the submaxillary gland may be situated entirely on the inner surface of the mylohyoid muscle Very rare abnormalities include hypertrophy of the parotid the sublingual glands or the glands of Nuhn and Blandin duct abnormalities external fistulae of the parotid and congenital ranulae of the floor of the mouth

Congenital tumours

Such tumours are rare The commonest is a haemangioma of the parotid either capillary or cavernous in type (Fig 13) *Lymphangioma of the parotid is less* common There have been a few cases of congenital cysts mixed tumours and carcinoma of the parotid

MUMPS

This acute specific infectious disease is characterized by inflammation of the salivary glands especially the parotid and less often the other salivary glands and by a tendency to be complicated by metastatic inflammation of the testes and much

CHAPTER 5

DISEASES OF THE SALIVARY GLANDS

REGINALD T PAYNE

SPECIAL METHODS OF INVESTIGATION

THE FOLLOWING special examinations are applicable to diseases of the salivary glands

Mixed saliva

Investigation of mixed buccal saliva is of limited value

Cannula saliva

The examination of cannula specimens of parotid saliva may be of great assistance in diagnosis Normal parotid saliva is clear and watery but in pyogenic infections turbidity may be due to the presence of pus mucopus epithelial cells and bacteria Normal submaxillary saliva is faintly turbid owing to the presence of mucus The best type of cannula is a fine glass one with the tip drawn out to 1 millimetre diameter and a fountain pen bulb attached to the other end

Ptyalin

The quantitative estimation of ptyalin has little clinical application The qualitative determination may be important in establishing the diagnosis of an external salivary fistula

Cytology

Normal parotid secretion may show an occasional epithelial cell but in catarrhal conditions of the gland and ducts there may be large numbers of epithelial cells and of pus cells

Bacteriology

Material for bacteriological examination can be collected in a fine glass cannula from the parotid duct after swabbing the region with spirit Anaerobic cultures should always be made and tests for penicillin sensitive organisms may be valuable

Probing the ducts

This may be of great value in the case of the parotid duct both for the localization of calculi the determination of strictures and as a method of dilatation The most useful types of dilators are Liebreich s straight lacrimal probes or Bowman s or Couper s bulbous ended and slightly curved nasal duct probes

Clinical picture

The patient comes under observation on account of a swelling in the floor of the mouth In some instances the swelling after developing for a few days suddenly ruptures with the discharge of a material like egg white into the mouth After a period of quiescence the enlargement and rupture again occur

Examination reveals a purplish thin walled swelling in the anterior part of the floor of the mouth running over the surface of which are numerous fine blood vessels The swelling may be to one side of the mid line if very small but in most cases it reaches beyond this limit or encroaches upon the inferior aspect of the tongue The corresponding submaxillary duct is usually displaced and the distortion of the parts may render it impossible to find the duct orifice A ranula of the gland of Nuhn and Blandin is confined to the inferior aspect of the tongue Ranulae may interfere with a lower denture

Operative treatment

Complete excision is usually impossible owing to the difficulty of identifying the submaxillary duct Under general anaesthesia the superficial part of the cyst should be excised and the cavity swabbed with 1 per cent zinc chloride solution to destroy the remaining cells The cavity should then be packed with gauze for 48 hours and one cat gut suture may be advisable Healing occurs by granulation Ranulae of the gland of Nuhn and Blandin should be excised together with the underlying gland Burrowing ranulae require an extensive combined buccal and external operation

Prognosis and results of treatment

Occasionally a ranula appears once or twice and then after rupturing completely clears up This however is unusual Operative treatment gives excellent results provided the mucosal lining has been destroyed

MIKULICZ S DISEASE AND SYNDROME

Mikulicz s disease and Mikulicz s syndrome refer to chronic bilateral enlargements of the parotid and other paired salivary glands and often of the lacrimal glands

Aetiology

Mikulicz s disease proper may be familial or acquired but the aetiological factor is unknown A familial type of the disease known as mangy occurs in Madagascar In Mikulicz s syndrome the enlargement of the salivary glands is a local manifestation of a general disease for example leukaemia tuberculosis syphilis (?) lymphosarcoma toxaemia due to lead iodides and similar substances gout (?) the uveoparotid syndrome and Boeck s sarcoid

Morbid anatomy

In Mikulicz s disease proper the affected glands are diffusely infiltrated with lymphoid cells mainly round the walls of the alveoli In Mikulicz s syndrome the glands show the characteristic changes of the underlying disease

less often of other parts of the sexual organs of both sexes It will not be considered further except in relation to differential diagnosis

RANULA

The term ranula is an ill defined one which is applied to cystic swellings of the floor of the mouth and under surface of the tongue caused by blockage of small salivary glands



FIG 13 —Haemangioma of left parotid in an infant aged 9 months The condition was first noticed at the age of 4 months

Aetiology

Congenital ranulae have been described but are very rare In the usual acquired type the exact aetiological factor cannot often be determined A small group is traumatic in origin and minute fragments of wood bristles or similar substances may block the orifice of a mucous gland or submaxillary duct A ranula may also follow dental treatment infection or operation on the floor of the mouth

Surgical anatomy and pathology

The usual ranula consists of a superficial part composed of buccal mucosa lined by a flattened layer of epithelial cells and a deeper part consisting of the wall of the cyst adherent to the subjacent tissues The term burrowing ranula is applied to large cysts which involve the floor of the mouth and the submental and submaxillary regions possibly by extension through the mylohyoid muscle A ranula may also affect the gland of Nuhn and Blandin on the under surface of the tongue

Clinical features

The majority of these conditions merit no further consideration Irradiation for malignant disease of the buccal cavity nasopharynx and similar sites may lead to extensive destruction of salivary gland tissue and the resulting dryness of the mouth frequently causes severe discomfort Many patients are obliged to suck sweets during the day and to take water throughout their meals

Surgical diseases of the salivary glands are rarely sufficiently widespread to cause xerostomia except in chronic and recurrent pyogenic infections involving all the large salivary glands

A small group of cases occurs in which progressive xerostomia is probably nervous in origin In the worst cases this is ultimately followed by rapid dental caries cracking and suppuration of tissues of the mouth and an agonizing death

Some patients complain of dryness of the mouth but clinical examination does not give objective support to this In such cases there is often a background of anxiety which has coincided with some temporary or even trivial buccal disease (such as irritation caused by new dentures)

Treatment

Treatment must be based on the cause If the cause cannot be eradicated then the treatment must be purely symptomatic When the condition is associated with widespread inflammatory disease treatment of the infection may relieve the xero stomia Reassurance may help those patients where there is a functional element

PTYALISM OR SALIVATION

Ptyalism or salivation is a condition in which an excessive amount of saliva collects in the mouth and causes discomfort

Aetiology

Like xerostomia ptyalism is not a disease but a symptom of many diseases It may be either true or false according to whether there is some disturbance in swallowing which causes the saliva to dribble from the mouth

True ptyalism

True ptyalism may occur in the following conditions

1 Local disease of the mouth gums usually of an inflammatory nature
2 As a reflex
    (a) in diseases of the oesophagus stomach or duodenum
    (b) in pregnancy
    (c) in trigeminal neuralgia
3 In nervous diseases such as bulbar paralysis or encephalitis lethargica
4 In acute specific fevers such as smallpox or hydrophobia
5 In disease of the salivary glands such as syphilitic parotitis
6 In the insane as in general paralysis of the insane or melancholia
7 As the result of drugs such as mercury pilocarpine and iodides
8 In pellagra

Clinical picture

In Mikulicz s disease proper the enlargement of the parotids is chronic *bilateral* and painless and the other salivary glands and the lacrimal glands are usually involved In Mikulicz s syndrome variations occur which depend on the aetiological factors

Course and prognosis

Mikulicz s disease proper causes little inconvenience apart from the deformity and occasionally a dryness of the mouth It does not shorten life The prognosis in Mikulicz s *syndrome depends on the causal disease*

Diagnosis

A diagnosis of Mikulicz s disease proper should not be made until the various diseases which may give rise to the syndrome have been excluded In the past cases were confused with bilateral recurrent parotitis with involvement of the submaxillary glands

Treatment

X ray treatment is the only measure likely to reduce the size of the glands in Mikulicz s disease proper In Mikulicz s syndrome the underlying disease must be treated

XEROSTOMIA OR APTYALISM

Xerostomia is the condition in which there is a marked diminution of salivary *secretion*

Aetiology

Xerostomia is not a disease in itself but is a feature of many diseases The term should be reserved for cases in which actual dryness of the mouth is present and not used merely because one or more of the larger salivary glands shows atrophy True xerostomia usually means that some pathological process is at work which is affecting not only the large salivary glands but also the numerous small ones This *process* includes both structural lesions and functional disturbances The condition is almost always an acquired one and may occur in any of the following conditions

1 Severe fever
2 Severe sweating
3 Severe diarrhoea (cholera dysentery)
4 Severe diuresis (diabetes mellitus diabetes insipidus)
5 Uraemia
6 Poisoning from such as atropine and stramonium
7 Senile atrophy of salivary glands
8 Atrophy following radiation
9 Atrophic changes in the salivary glands following local disease but involving many glands (such as Sjogren s syndrome chronic infection)
10 In anxiety states or in great emotion

tender constitutional disturbance is severe there is often redness and oedema round the orifice of the duct and in the absence of complete duct obstruction pressure over the gland may produce a flow of pus into the mouth (Fig 14)

Course and prognosis

The prognosis is partly governed by the prognosis of the associated condition but the parotitis may prove the determining factor Staphylococcal infections are the most serious because they tend to be carbuncular Danger to life is greatest when the duct is completely obstructed



FIG 14—Acute suppurative parotitis and subcutaneous abscess The parotitis was secondary to radium treatment of a carcinoma of the buccal aspect of the right cheek The capsule of the gland has ruptured in the lower and anterior part and given rise to a large subcutaneous abscess This was drained and the pus contained a pure growth of *Staph aureus* (*By courtesy of Royal Society of Medicine*)

Diagnosis and differential diagnosis

An attempt should be made to obtain parotid secretion for examination either by expression into the mouth or by catheterization of the duct Mumps may cause confusion but a history of contact must be sought more than one salivary gland is usually involved second attacks are curiosities and there is no gross change in the saliva Inflammatory swellings of the lower jaw cheek or pre auricular lymph nodes may simulate acute parotitis

Treatment

This should begin as soon as possible because active measures in the early stages may avert operation The diet should be as solid as the patient can manage and chewing should be encouraged Dry heat should be used externally and hot mouth washes internally Gentle massage of the gland in a forward direction in the line of the duct may empty it of retained secretions This procedure may be assisted by probing the duct or by catheterization and aspiration Danger to life is not usually great if pus can thus be emptied into the mouth Full doses of penicillin should be given in all cases and penicillin lozenges should also be used

Operation is indicated when there is exquisite tenderness over the gland oedema of the overlying tissues the persistence of high fever with absence of duct secretion for more than 24 hours failure to respond to penicillin and any evidence of gross abscess formation

False ptyalism

False ptyalism occurs in conditions where the swallowing mechanism is interfered with such as bilateral facial paralysis tic douloureux and in functional conditions

Clinical picture

Excessive saliva may cause serious local discomfort In the worst cases it makes *life miserable by necessitating the patient s carrying about a receptacle into which* to deposit his saliva and by disturbing sleep

Diagnosis and treatment

As ptyalism is rarely due to primary disease of the salivary glands attention must never be too sharply focused on these organs Specific treatment is rarely called for but any underlying disease must be treated When the primary disease cannot be cured or where symptoms are severe and no cause can be found treatment may justifiably be directed to the salivary glands Atropine may be of some value but x ray therapy should be reserved for the worst cases

ACUTE PAROTITIS

(*Synonyms* Acute pyogenic parotitis acute suppurative parotitis acute non epidemic parotitis acute sialodochitis)

Aetiology and pathology

Acute parotitis is invariably an ascending infection from the buccal cavity especially in conditions accompanied by dryness of the mouth impaired mastication and alteration in the local bacteria The chief of these conditions are buccal or pulmonary infections acute specific fevers septicaemia uraemia peptic ulceration especially during medical treatment and the post operative state particularly after operations on the alimentary tract Cases secondary to a parotid calculus or recurrent parotitis form small but important groups Acute parotitis may develop by direct extension as in osteomyelitis of the mandible but haematogenous infection is extremely rare Even in septicaemic conditions a parotitis is usually an ascending infection The *Staphylococcus aureus* is the commonest organism but the haemolytic *Streptococcus pyogenes* the *Str viridans* and the pneumococcus are occasionally responsible

The infective process starts in the lumen of the main duct which becomes obstructed by exudate and secretion ascends through the smaller ducts to reach the acini and then extends through their walls giving rise to multiple minute abscesses Some of these may become confluent and rupture the parotid fascia into the external auditory meatus pharynx and temporo mandibular joint The gland may be enlarged to 6 or 8 times its normal size Infections due to the *Str viridans* are rarely very acute and do not lead to abscess formation

Clinical picture

In the catarrhal stage there is moderate fever and the gland is painful slightly *swollen* and tender In the suppurative stage with miliary or confluent abscesses the gland is grossly enlarged the subcutaneous tissues are oedematous and very

in cases due to the *Str viridans* The individual attacks do not usually start during meals but patients often report that the beginning of an attack has been noted on waking



Fig 15 —Bilateral recurrent parotitis From a man of 32 years of age with a 7 years history of parotid swellings he came under observation as a case of bilateral parotid tumours The saliva from both parotid glands was turbid and gave a pure growth of *Str viridans* (*By courtesy of Royal Society of Medicine*)

Course and prognosis

Suppuration is almost unknown owing to the nature of the infecting organisms The parotid gland may remain much enlarged for many months The attacks often tend to become more frequent and more severe

Diagnosis

This rests upon the clinical picture the examination of the saliva and the results of sialography A cannula specimen of saliva is usually turbid owing to blobs of mucopus and microscopically reveals epithelial and pus cells Cultures should be made

After straight radiographs have excluded calculi iodized oil should be injected into the duct Globular or ovoid dilatations of various sizes may be present in the finest ducts and segmental or fusiform dilatations in the larger ducts (Figs 16 and 17)

Differential diagnosis

The condition is still confused with mumps Mikulicz s disease mixed tumour or dental disease of the mandible

Treatment

In the milder forms it may be possible to keep the patient almost free from attacks by getting him to massage the parotid in a forward direction and in the line of the duct for about 5 minutes every morning and evening with the object of emptying the duct Any cause of buccal infection should be treated and imperfect occlusion or ill fitting dentures adjusted In children allergy should be considered

Operative technique

The gland is best exposed by a curved incision starting at the level of the zygomatic bone and passing downwards immediately in front of the ear behind and below the angle of the jaw and then forwards to the anterior border of the masseter muscle The skin and subcutaneous tissues are dissected forwards and the gland exposed Five or six radiating incisions are then made into the parotid *fascia in the line of the branches of the facial nerve* and the deeper parts of the gland are opened with Spencer Wells forceps It is unusual to find any gross collection of pus but within 24 hours or so the wounds discharge freely The incision described exposes the gland adequately gives excellent drainage and a negligible scar Penicillin treatment has rendered early secondary suture possibl

Complications

Facial paralysis may occur during very acute attacks A salivary fistula is a rare complication of operation Acute parotitis may occasionally be a precursor of recurrent parotitis or lead to the rare auriculo temporal syndrome

RECURRENT PAROTITIS

(*Synonyms* Recurrent pyogenic parotitis recurrent sialodochitis recurrent enlargem nt of the parotid)

Aetiology and pathology

The disease is a chronic infection of the ducts causing recurrent exacerbations with swelling of the gland The condition is commonest in women In most cases there is a dental factor leading to impaired mastication and in many cases there is a psychological background The dental factor is either some permanent or temporary derangement of the chewing mechanism caused by buccal disease dental treatment or ill fitting dentures The psychological disturbance is rarely a serious one but I have seen many patients in whom the original attack or recurrent exacerbations had corresponded accurately with a very real anxiety The condition occasionally follows acute parotitis An allergic basis has been suggested for some of the cases in infancy

The Str viridans is the commonest organism with the pneumococcus second in importance Catarrhal infection of the ducts causes the normal watery secretion to become thick and tenacious and from time to time obstruct the ducts and lead to *various types of dilatation and irregularity*

Clinical picture

The condition is usually unilateral but it may become bilateral and even involve the submaxillary glands (Fig 15) *Patients may come under observation in the* initial attack or only after attacks have been present for years Between the attacks of retention the gland is not necessarily enlarged but its limits are often palpable and it may be slightly tender From time to time the gland becomes swollen and tender and after remaining in this condition for several days or even we ks gradually subsides The frequency and severity of the acute exac rbations vary within wide limits fever is rarely marked and constitutional disturbance is slight

in cases due to the *Str. viridans*. The individual attacks do not usually start during meals but patients often report that the beginning of an attack has been noted on waking.



Fig. 15.—Bilateral recurrent parotitis. From a man of 3? years of age with a 7 years history of parotid swellings. He came under observation as a case of bilateral parotid tumours. The saliva from both parotid glands was turbid and gave a pure growth of *Str. viridans*. (*By courtesy of Royal Society of Medicine.*)

Course and prognosis

Suppuration is almost unknown owing to the nature of the infecting organisms. The parotid gland may remain much enlarged for many months. The attacks often tend to become more frequent and more severe.

Diagnosis

This rests upon the clinical picture, the examination of the saliva and the results of sialography. A cannula specimen of saliva is usually turbid owing to blobs of mucopus and microscopically reveals epithelial and pus cells. Cultures should be made.

After straight radiographs have excluded calculi, iodized oil should be injected into the duct. Globular or ovoid dilatations of various sizes may be present in the finest ducts and segmental or fusiform dilatations in the larger ducts (Figs. 16 and 17).

Differential diagnosis

The condition is still confused with mumps, Mikulicz's disease, mixed tumour or dental disease of the mandible.

Treatment

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(*Synonyms* Recurrent pyogenic parotitis recurrent sialodochitis recurrent enlargem nt of the parotid)

Aetiology and pathology

The disease is a chronic infection of the ducts causing recurrent exacerbations with swelling of the gland The condition is commonest in women In mo t cases there is a dental factor leading to impaired mastication and in many cases there is a psychological background The dental factor is either some p rmanent or temporary derangement of the chewing mechanism caused by buccal disease *dental treatment or ill fitting dentures The psychological disturbance is rarely* a serious one but I have seen many patients in whom the original attack or recurrent exacerbations had corresponded accurately with a very real anxiety The condition occasionally follows acute parotitis An allergic basis has been suggested for some of the cases in infancy

The *Str viridans* is the commonest organism with the pneumococcus second in importance Catarrhal infection of the ducts causes the normal watery secretion to become thick and tenacious and from time to time obstruct the ducts and lead to various types of dilatation and irregularity

Clinical picture

The condition is usually unilateral but it may become bilateral and even involve the submaxillary glands (Fig 15) Patients may come under observation in the initial attack or only after attacks have been present for years Between the attacks of retention the gland is not necessarily enlarged but its limits are often palpable and it may be slightly tender From time to time the gland becomes swollen and tender and after remaining in this condition for several days or even we ks gradually subsides The frequency and severity of the acute exacerbations vary within wide limits fever is rarely marked and constitutional disturbance is slight

CHRONIC PAROTITIS

Treatment of the more severe cases must be determined after adequate investigations Slitting and dilatation may be of great value if there is evidence of marked obstruction of the main duct but the dilatation must be continued until all tendency to contraction has passed Penicillin treatment may also be indicated The results of auriculo temporal avulsion are uncertain X ray treatment is of value in some of the milder cases due to the *Str viridans* and in the absence of gross duct obstruction A really acute exacerbation may be due to the development of secondary infection

PNEUMOCOCCAL PAROTITIS

Pneumococcal parotitis occupies a position midway between the acute parotitis due to the *Staph aureus* and the typical recurrent parotitis due to the *Str viridans* The pneumococcal variety tends to occur as a recurrent type of enlargement of the parotid but the individual attacks are often quite acute and associated with high fever constitutional disturbance and much local pain and swelling In some cases the acute attack may be very severe and pass on to suppuration abscess or fistula formation. In established cases sialograms show gross dilatation of the major ducts and irregular dilatation of the finest ducts and acini The prognosis is good as to life There is much uncertainty as to the frequency and severity of the recurrent attacks Treatment has been described in the sections dealing with Acute and Recurrent Parotitis and its application must be determined according to the state of affairs present in each case

CHRONIC PAROTITIS

Aetiology and pathology

Chronic parotitis may be either pyogenic or specific Chronic pyogenic infections occasionally follow acute parotitis but are more likely to be late stages of recurrent parotitis or to be associated with a calculus

The specific infections causing chronic parotitis include tuberculosis syphilis and actinomycosis but all are extremely rare and with the exception of syphilis usually start outside the parotid

Diagnosis

The most careful investigations of both local and general conditions are necessary The local investigations must include radiography sialography the cytology and bacteriology of the saliva and occasionally biopsy (Fig 18) The nature of the general investigations must be determined by the associated clinical manifestations At times the physical signs may closely simulate malignant disease

Treatment and prognosis

In the pyogenic group those cases secondary to a parotid calculus are the most favourable for the infection usually subsides after removal of the calculus The cases secondary to acute or recurrent parotitis may require operation to overcome duct obstruction or x ray treatment to diminish catarrhal changes Specific parotitis may require both general and local treatment



FIG 16—Recurrent parotitis Right sialogram from patient in Fig 15 (*By courtesy of Royal Society of Medicine*)



FIG 17—Recurrent parotitis From a woman aged 45 years who developed parotitis following influenza 12 years previously The condition after persisting for some time gradually cleared up She came under observation 12 years later with a further attack of parotitis The saliva was extremely profuse and turbid and gave a profuse growth of Pfeiffer's bacillus (*By courtesy of Royal Society of Medicine*)

Clinical picture

The characteristic syndrome develops weeks or even months after the original parotid lesion Hyperaemia and sweating in the affected area develop in response to eating and as the result of a taste reflex from the posterior third of the tongue Tingling or even pain may appear at onset and the sweating may be enough for the moisture to trickle off the face In the worst cases the patient has to wear a towel round his neck during meals I have seen marked hyperaemia and moderate sweating 30 years after parotitis In the individual patient the area of involvement remains constant

Prognosis

Once established the condition persists but the amount of sweating may diminish with age

PAROTID CALCULI

Aetiology and pathology

Parotid calculi are rare submaxillary calculi being about 40 times as common The causes of precipitation of salts from the saliva are unknown The calculi are usually single and vary in size from 1 to 5 millimetres in diameter They are composed of calcium carbonate calcium phosphate and traces of organic materials The calculi are situated either in the main or smaller ducts and dilatation take place behind them Some degree of infection is constantly present

Clinical picture

Patients come under observation on account either of recurrent enlargement of the gland or of acute recurrent or chronic parotitis The enlargement occurs during meals and subsides soon afterwards and is accompanied by a feeling of tightness Residual swelling is unusual Minute calculi may be passed spontaneously Untreated calculi sooner or later lead to complications

Diagnosis

Clinical confirmation may sometimes be obtained by palpation of the masseteric or buccal portions of the duct or even of the gland itself Acid fruits may cause swelling of the gland Stereoscopic radiographs should be made but the detection of calculi is notoriously difficult (Fig 19) A catheter specimen of saliva should be examined to determine the nature of the infection Sialography should be performed if the diagnosis is still in doubt It is important to remember the rarity of parotid calculi and the much greater frequency of recurrent parotid enlargement due to infection of the duct system

Treatment

Calculi in the buccal portion of the duct may be removed by incision of the medial wall of the duct from within the mouth Those in the masseteric portion or in the intraglandular ducts must always be approached externally through a free exposure of the gland and duct The wound must be closed in layers to prevent the formation



FIG 18—Chronic parotitis with monilia infection of buccal cavity Right sialogram showing gross dilatation of main duct From a boy aged 16 years who had had recurrent ulceration of his mouth from infancy *(By courtesy of Royal Society of Medicine)*

AURICULO TEMPORAL SYNDROME

(Frey s syndrome or local hyperidrosis of the face)

Aetiology

The syndrome is a rare complication of suppurative parotitis or injury of the parotid or its vicinity and leads to a condition of hyperaemia and sweating of the auriculo temporal area of the face and scalp Most of the reported cases occurred in Poland and Russia and followed parotitis during the course of typhus or typhoid fever A few have been reported following gunshot wounds operations for mixed tumours or in syringomyelia

Surgical anatomy

The area of involvement is characteristically that supplied by the auriculo temporal nerve and less often the areas supplied by the third division of the fifth nerve and the great auricular nerve

Pathology

The evidence suggests that the phenomena are reflex and result from the establishment of connections between parotid secretory fibres of the auriculo temporal nerve and vasomotor and sweat secretory fibres running through the same nerve These abnormalities may follow division of the nerve or be secondary to inflammation

PAROTID FISTULAE

Clinical picture

Obstruction of the duct causes retention of saliva and enlargement of the gland and predisposes to ascending infection Functional obstruction generally occurs in highly strung patients and they find relief by pressure on the cheek which forces the retained saliva into the mouth

Diagnosis

This must be based on the history clinical examination probing the duct cytological and bacteriological examination of the saliva skiagrams and sialo graphy

Treatment

This must be determined by the nature of the underlying cause Functional obstruction may be cured by a plastic operation on the orifice and buccal portion of the duct

PAROTID FISTULAE

Aetiology and pathology

Internal fistulae are unimportant External fistulae are caused by injury ulceration or infection involving the duct its branches or the gland or they may arise secondary to disease in adjacent structures The condition may follow operations upon the mastoid temporo mandibular joint or cheeks

Clinical picture

The saliva pours out through the external fistula The secretion is aggravated during meals and it may be copious in the case of a fistula involving a large duct The external opening is usually pin point in size and the adjacent skin is inflamed If a fistula should close spontaneously the scar usually breaks down

Diagnosis

The secretion should be examined for ptyalin Sialography is of value in determining whether a fistula is connected with the main duct or with one of its branches or is merely glandular It is important to know whether there is any associated stenosis of the main duct or infection of the saliva

Treatment

The cause and site of the fistula must be considered Fistulae associated with calculi or with malignant disease cannot heal until these conditions have been treated and no fistula will heal in the presence of duct stenosis Many operations have been devised for fistulae of the main duct with the object either of reconsti tuting the duct or of converting an external into an internal fistula In the past they frequently failed owing to post operative infection Penicillin treatment should eliminate this risk Parotid function should be depressed after all plastic procedures (*see* Parotid Calculi) Glandular fistulae usually heal after excision of the fistulous tract the application of the electro cautery and careful

of a fistula Endotracheal anaesthesia is essential and the use of penicillin cover important When an external approach has been used the activity of the parotid should be depressed by bandaging the jaws limiting talking and by a bland fluid diet at body temperature



FIG 19 —Left parotid calculus associated with chronic parotitis (*By courtesy of Royal Society of Medicine*)

Acute parotitis secondary to a calculus should be treated on the lines already indicated Unless the calculus is actually situated at the duct orifice there should be no attempt to remove it until the acute stage is over

OBSTRUCTION OF THE PAROTID DUCT

Aetiology and pathology

The commonest cause of obstruction is a recurrent parotitis with inflammatory changes in the saliva leading to the formation of mucous plugs in the ducts In some cases the sialodochitis leads to narrowing of the main duct Obstruction due to a parotid calculus is described on page 99

The duct may occasionally be obstructed by mixed tumours in its walls or by primary carcinoma Mixed parotid tumours or adjacent tumours often press on and deform the ducts but rarely cause obstructive symptoms Obstruction and gross dilatation of the duct may occur without any organic lesion or infection An allergic basis has been suggested

obstruction Relief of the obstruction leads to a gush of pus into the mouth In the case of calculi in the posterior part of the duct or in the hilum of the gland no attempt at surgical excision of the gland should be made during the acute phase

General lines of treatment are also called for Penicillin should be used in full doses The severe pain is helped by the use of dry heat externally and by frequent hot mouth washes An emergency tracheotomy may be required if there is much cellulitis If the acute infection has been secondary to a calculus in the gland or the posterior part of the duct excision of the gland should be carried out 2 or 3 months after the acute condition has subsided This operation may be technically difficult owing to fixation of the gland to the hyoglossus muscle and to the lingual and hypoglossal nerves

CHRONIC SUBMAXILLARY SIALOADENITIS AND SIALODOCHITIS

Aetiology and pathology

Chronic submaxillary sialoadenitis and sialodochitis are late stages of obstruction and infection of the duct system They are commonest as a sequel of calculous disease but may follow other types of duct obstruction or be chronic from the out set or associated with recurrent parotitis

The gland becomes more globular It is firm in consistency and histologically shows replacement fibrosis round celled infiltration and dilatation and catarrh of the ducts

Clinical picture

The patient comes under observation on account of a persistent submaxillary swelling and there is usually a long standing history of typical meal time swelling or insidious increase in size of the gland Clinical examination reveals a visible swelling which is firm slightly tender not attached to the skin and is movable or partially movable over the deeper tissues Bi digital examination may reveal calculi within the gland or duct or other local disease

Diagnosis and differential diagnosis

X ray examination should be carried out Mixed or malignant tumours of the submaxillary gland are the conditions most likely to cause confusion as both may give a history of a slowly increasing swelling and very similar physical signs It must be remembered that tumours of the gland are rare while calculous disease is common

Prognosis

Chronic infections gradually destroy glandular function Acute infection may supervene especially if obstruction is present

Surgical treatment

The gland should be excised in all cases associated with calculi in the hilum or posterior part of the duct for a persisting local tumour and in cases where the diagnosis is uncertain

closure of the wound It may be possible to diminish glandular activity by deep x ray treatment or by auriculo temporal avulsion if operative treatment is contra indicated

ACUTE SUBMAXILLARY SIALODOCHITIS AND SIALOADENITIS

Aetiology and pathology

Acute infection of the duct system is invariably secondary to obstruction usually due to calculi Less common causes are scarring of the duct or floor of the mouth or carcinoma The duct system rapidly becomes distended with infected saliva and there is a great tendency for the infection to involve the cellular tissues of the floor of the mouth and neck The submaxillary lymphatic nodes which are mostly within the capsule of the gland are involved and may suppurate Acute infections of the submaxillary duct system are potentially serious and are one of the causes of Ludwig s angina Most infections are due to the *Staph aureus*

Clinical picture

The patient comes under observation with a painful swelling in the submaxillary region and floor of the mouth and a history of obstructive submaxillary symptoms The constitutional symptoms may be severe and there is considerable difficulty in opening the mouth and swallowing The submaxillary region is enlarged and is occupied by an ill defined painful tender and oedematous swelling If the obstruction is near the duct orifice there may be redness and oedema in the line of the duct, while if the obstruction is at the hilum of the gland there may be little change in the mouth Pressure on the submaxillary region may force pus into the mouth

The prognosis is usually good but all cases are potentially serious owing to the risks of cellulitis and oedem i of the glottis In calculous cases one attack of acute infection predisposes to another and the resulting matting of the tissues makes excision of the gland difficult

Diagnosis and differential diagnosis

An x ray examination should be carried out to determine the site and number of any calculi Any pus should be examined bacteriologically

The condition is most likely to be confused with acute dental infections of the *mandible alveolar abscesses osteomyelitis or with other causes of submaxillary* lymphadenitis

Treatment

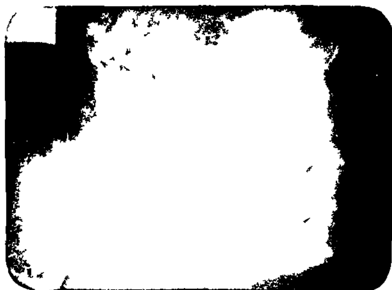
Surgical intervention is called for where a calculus or stricture is situated in the anterior part of the duct or on account of abscess formation within the submaxillary gland the submaxillary *lymph nodes or adjacent tissues*

Operations should be carried out under general anaesthesia If a calculus is situated in the anterior part of the duct it is best to cut directly down on to it and remove it When the calculus is extremely small and when the obstruction is due to stricture the distended duct should be incis d immediately behind the



(a)

FIG .0.—(a) Submaxillary duct calculus (b) large calculus in posterior third of the submaxillary duct (*By courtesy of the Royal Society of Medicine*)



(b)

SUBMAXILLARY CALCULI

The term salivary calculus is applied in its widest sense to calcareous deposits found on the teeth on dentures in the salivary ducts or on the buccal surface of the cheeks In general surgical usage the term is confined to calculi occurring in the salivary glands or ducts

Aetiology

Submaxillary calculi are about 40 times commoner than those of the parotid The evidence as to bacterial origin is lacking and if infection were a factor calculi should be commoner in the parotid Bacteria are frequently present in the nucleus of calculi but the part they play is probably in altering the reaction of the saliva The relative frequency of submaxillary calculi is probably related to the high mucin content of submaxillary saliva

Structure of calculi

The calculus may be a minute structure smaller than a pin s head and occasionally large numbers of such calculi are present The characteristic date stone calculus is far from being the commonest type Multiple faceted calculi may occur in the gland or duct while a large rounded or branched calculus may develop at the hilum of the gland Calculi consist chiefly of calcium carbonate with small amounts of calcium phosphate soluble salts and organic matter

Clinical picture

Patients with calculous disease may present the following clinical pictures

1 Swelling of the submaxillary gland and possibly of the floor of the mouth while eating associated with discomfort or pain The submaxillary swelling gradually subsides to recur again with the next meal
2 A persistent submaxillary swelling not varying with meals which has developed suddenly or gradually or as the end stage of a meal time syndrome
3 The spontaneous discharge of a calculus through the duct orifice its presentation at the orifice or ulceration through the duct
4 Acute infection of the duct and gland
5 Suppurative cervical lymphadenitis secondary to infection
6 Ludwig s angina
7 Clinical quiescence and discovery during clinical or radiographic examination

Diagnosis and differential diagnosis

Clinical diagnosis is not usually difficult if the regions of the gland and duct are palpated bi digitally and if the floor of the mouth is inspected thoroughly to see the nature of any secretion coming from the ducts

Intra oral and extra oral skiagrams should be taken but a negative result does not necessarily exclude a calculus (Fig 20 (*a*) and (*b*)) Submaxillary calculi are often confused with dental conditions of the mandible with submaxillary lymphadenitis and occasionally with tumours of the gland

SUBMAXILLARY DUCT OBSTRUCTION

Aetiology and pathology

Obstruction of the outflow of saliva may result from changes in the lumen or wall of the duct or in the tissues outside the duct The following are the commonest causes calculi recurrent or chronic sialodochitis scarring of the duct following injury operative trauma the passage of a calculus some types of ranula ulceration or diseases of the floor of the mouth such as carcinoma and the scarring following radium treatment The gland undergoes replacement fibrosis

Clinical picture

Obstruction of the salivary outflow causes enlargement of the gland At first this enlargement is aggravated by eating but in time this functional variation ceases Acute or chronic inflammation may supervene

Diagnosis

The nature and site of the obstruction must be determined by clinical examination x rays sialography and probing of the duct

Treatment

This must depend upon the cause The treatment of calculous obstruction has been described In the case of obstruction due to scarring a fistulous opening may be created in the duct behind the obstruction Cases associated with recurrent or chronic sialodochitis should be treated by excision of the gland

DISEASES OF THE SUBLINGUAL GLANDS

Diseases originating in or involving the sublingual salivary glands are rare but the following occur

1 *Mumps*
2 *Acute infection* —The glands may be involved in inflammatory processes of the floor of the mouth arising in the submaxillary duct or as part of Ludwig s angina Treatment must be directed to the whole inflammatory process but incision of the sublingual glands may be necessary
3 *Recurrent and chronic infection* —The glands may be involved alone or as part of a process involving all the large salivary glands Excision may be necessary especially if the glands interfere with lower dentures
4 *Calculi* —Calculi rarely occur in the sublingual glands or ducts but have been recorded in infants
5 *Mikulic s disease* —The glands may be involved in any of the conditions which lead to Mikulicz s disease or Mikulicz s syndrome
6 *Mixed tumours* — These are extremely rare and are much less common than such tumours of the upper lip
7 *Malignant disease* —Primary malignant disease is rare and up to 1939 only 11 cases had been recorded
8 *Ranula* —The common type of sublingual ranula starts either in the mucous glands of the floor of the mouth or in the sublingual gland itself Clinically the two types cannot usually be distinguished

Prognosis

A minute calculus may pass spontaneously However as long as a calculus is present the greatest risk is that acute infection will supervene and that this may be of the nature of cellulitis or Ludwig s angina

Indications for surgical intervention

Surgical intervention is called for in almost all cases on account of the risks of progressive obstruction and of infection

Operative technique

Calculi in the anterior part of the duct

These should be approached through the floor of the mouth Surface anaesthesia with 10 per cent cocaine may be adequate or it may be combined with infiltration with 1 per cent Novocain Endotracheal anaesthesia is advisable for calculi which are not close to the duct orifice When a calculus is wedged at the duct orifice the region should be lifted up with dissecting forceps and the duct orifice excised obliquely together with the calculus In the case of a calculus in the anterior third of the duct but not at the orifice the tissues behind the calculus should be fixed by dissecting forceps and an incision made directly over the calculus

Calculi in the hilum of the gland or posterior part of the duct

These can only be treated by excision of the gland and the posterior part of the duct through an external approach When inflammation has occurred the gland is fixed to the tissues and dissection of the deep part of the gland from the hyoglossus muscle and lingual and hyoglossal nerves may be difficult The considerable cavity left between the side of the tongue and the medial aspect of the mandible must be drained Penicillin cover is indicated

Cases with acute infection

When acute infection develops treatment must be primarily directed to the infection In the case of a calculus in the anterior part of the duct it is possible by removal of the calculus to release the infection No such simple treatment is possible when infection supervenes with a calculus in the gland or posterior part of the duct Intensive penicillin therapy should be instituted as this may abort the infection but an abscess in the regional lymph nodes may require drainage Excision of the gland should be carried out after an interval of 2 or 3 months Cases which present with a condition of Ludwig s angina must be treated on the appropriate lines

Post operative care

Stenosis after operations on the anterior part of the duct is unusual but it may be advisable to dilate the new orifice occasionally during healing Excision of the submaxillary gland may damage branches of the facial nerve to the lower lip but a remarkable degree of recovery usually takes place with time

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MUCOUS CYSTS OF THE LIPS AND CHEEKS

Aetiology

Mucous cysts of the lips and cheeks appear to arise spontaneously but presumably have been preceded by trauma mild infection or inspissation of secretion The cysts are lined with mucous membrane surrounded by connective tissue and cellular infiltration

Clinical picture

The cysts are particularly prone to occur on the inner part of the lower lip or on the inner surface of the cheek On examination they are slightly projecting smooth rounded and soft swellings

Operative technique

They can be treated either by reflection of the overlying mucosa with complete dissection of the cyst and closure of the mucosa or by removal of the overlying mucosa and cyst wall leaving the inner wall of the cyst as the new mucosa

MACROCHEILIA OF LABIAL GLANDS

(*Synonyms* Hyperplasia of labial glands or glandular cheilitis)

This is a condition of increase in the mucous salivary glands in the lip often accompanied by mild chronic infection

Aetiology and pathology

The aetiology is unknown though in some cases the condition starts in child hood *There is marked hyperplasia of the labial glands especially in* the upper lip associated with a non specific cheilitis Actual fistula formation may be present

Clinical picture

The swelling of the upper lip may develop suddenly or gradually and there may be *a cycle of changes suggesting a periodic and superimposed inflammatory* element The condition persists or progresses in the absence of surgical treatment

Differential diagnosis

Diagnosis has to be made from inflammatory conditions and localized tumours *especially mixed tumours*

Treatment

The only effective method of treatment is a wedge shaped excision of the whole length of the upper lip from the mucosal aspect and including all the hyperplastic tissue

INNOCENT NON EPITHELIAL TUMOURS

Congenital tumours are discussed on page 87 Lipomas of the parotid are the only innocent connective *tissue tumours* of any importance and they are extremely rare They may be situated superficially between the capsule and the gland in the gland

tissue proper or between the gland and the pharynx In some cases the gland tissue is replaced by fat The symptoms and signs are those of a slowly growing parotid tumour and diagnosis is usually quite impossible until operation has been undertaken A fibrosing lipoma of the submaxillary gland has been describ d

MIXED SALIVARY TUMOURS

Mixed tumours form the most important and most frequent type of salivary gland tumours They arise in situations where salivary gland tissue exists and they have highly characteristic pathological and clinical features

Aetiology and sites

Nothing definite is known about aetiology The tumours usually start between 20 years and 40 years of age and they are equally common in the two sexes The parotid is by far the commonest site and growths here are about 10 times commoner than in the submaxillary gland Tumours of the hard or soft palate form a small but important group The less frequent sites include the upper lip the region of the tonsil the ampulla of the parotid duct the floor of the mouth the pharynx larynx and trachea the base of the tongue and the auditory meatus The sublingual gland is rarely involved

Pathology

The tumours vary in size from that of a pea to the huge growths described by older writers They are slightly lobulated and encapsulated the capsule being adherent to the adjacent glandular tissue The capsule may be incomplete and it may contain seedlings from which further growth takes place The tumours are firm or elastic and in cross section have a potato like appearance Myxomatous areas are common and undergo cystic degeneration or haemorrhagic infiltration

Histologically the tumours consist of the cellular elements proper and a myxomatous matrix The epithelial cells are arranged in sheets finger like processes or in acini There may be large areas of myxomatous material which is actually mucus secreted by the tumour cells In such areas the cells are scanty and resemble cartilage cells

The tumours are derived from glandular epithelium and should be regarded as adenomas They are certainly not mixed in the sense of being derived from more than one embryonic layer

The work of McFarland (1936) has shown that accurate histological classification is unsatisfactory Ahlbom (1935) has suggested that the only classification of value is that based on clinical macroscopic and microscopic features and one which includes both benign and malignant types On this basis it is possible to record growths as benign semi malignant or malignant

Clinical picture

The characteristic feature of mixed tumours is their slow painless growth Parotid tumours usually arise near the angle of the jaw and extend forwards or pass medially between the mandible external auditory meatus and the mastoid

process Large growths may interfere with the movements of the jaw they may cause deafness by pressure on the meatus or even facial palsy through stretching of the nerve

Physical examination reveals a visible well defined and slightly lobulated swelling (Fig 21(*a*)) The overlying skin is not attached to the tumour which however as it lies deep to the parotid fascia is not always freely movable The tumour may be firm elastic or soft Fluctuation is rare

Submaxillary tumours show similar physical signs but these may be somewhat masked by the relatively deeper situation (Fig 21(*b*)) Tumours in other situations show the essential characters modified by the local anatomical features

Course and prognosis

These observations refer to mixed tumours in all situations but especially to those of the parotid Most tumours increase in size gradually over many years growth rarely being completely arrested All are liable to carcinomatous change and even after 30 years or more a tumour may start to grow more rapidly and may become malignant Post operative recurrences grow more rapidly than the original tumour and there is an increasing risk of the growth being infiltrating in type The cause of the recurrence may be an incomplete removal of the original tumour rupturing of the capsule at operation the presence of microscopic seedlings or the fact that the tumour was multicentric in origin The risk of recurrence is greatest in the parotid owing to the anatomical considerations which determine surgery Recurrences are usually symptomless but there may be some fixation due to scarring

Diagnosis and differential diagnosis

The situations the symptomless growth and the physical signs usually establish the diagnosis Enlargements of the pre auricular or parotid lymph nodes resulting from chronic pyogenic infection or from tuberculosis may cause difficulty but pain tenderness or inflammation are usually present Skiagrams should be carried out in doubtful cases and sialography may help in distinguishing between innocent and malignant tumours Submaxillary tumours are often confused with calculous disease

ADENOLYMPHOMAS

Adenolymphomas form a rare type of salivary tumour with a highly characteristic histology They are also known as cystadenoma lymphomatosum epithelio lymphoid cyst and onkocytoma

Pathology

The tumours occur in or adjacent to any of the large salivary glands but are commonest in the parotid region The growths are encapsulated and their contents are soft friable and partly fluid The solid portions of the tumour consist of papillary processes covered with one or more layers of tall columnar epithelium set on a dense lymphoid stroma In the less typical cases the epithelial and lymphoid elements are blended irregularly

FIG 21 —(*a*) Mixed parotid tumour 1 ft from a man of 36 years of age—the tumour had been present for 4 years and had steadily increased in size (*b*) recurrent submaxillary tumour patient aged 43 years—the original tumour developed 10 years previously and was excised 6 years later The recurrence developed almost at once



(*a*)



(*b*)

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(a)



(b)

FIG 27—(a) Malignant parotid tumour left showing facial paralysis from a woman of 40 years of age in whom the condition had been present for 3 years—treatment by local excision and by irradiation had been carried out (b) malignant parotid tumour right patient aged 47 years—the condition started as a carcinoma of the right parotid duct

TREATMENT OF SALIVARY TUMOURS

Treatment may be by means of surgery or radio-surgery The indications for operation are the general principles of tumour removal the cosmetic and functional considerations and the inherent risk of malignancy in benign tumours

Radio surgery has been increasingly used in recent years owing to the high recurrence rate following operation but in view of the low radio sensitivity of salivary tumours as a whole they should be extirpated surgically whenever treat ment is indicated and excision appears practicable It is suggested that pre operative irradiation may toughen the tumour capsule and make excision easier it may possibly cure the tumour without operation and it may eliminate non salivary conditions McFarland (1936) Ahlbom (1935) Hybbinette (1935) and Patey (1940) all agree that it is unusual for benign tumours to show any appreciable diminution in size as the result of irradiation On the other hand some of the infiltrating tumours are extremely radio sensitive

Each case must be approached individually and the factors to be considered are the probable course of the untreated disease the limitations of surgery in the particular region and the problems confronting radiotherapy Expectant treatment may be justified in benign cases in later life or when the rate of growth is very slow

Clinical picture

This is identical with that of the usual mixed tumour but in some cases there is a suggestion of waxing and waning presumably owing to variations in the fluid content *In other cases again the tumours may be in the vicinity of* rather than incorporated in the larger glands Malignant transformation does not occur though local recurrences may follow incomplete operation

Treatment

This should be carried out on the lines indicated for benign tumours

MALIGNANT DISEASE OF THE SALIVARY GLANDS

Aetiology

Pathologically malignant disease forms no sharply defined group First it may develop in an old standing mixed tumour after many years of slow growth Secondly a mixed tumour recurrence may become malignant Thirdly a tumour of a semi malignant type may eventually become definitely malignant Finally malignant disease may develop as a primary condition Statistics reveal considerable *differences in the relative frequencies of the various types Primary malignant* tumours have a shorter history than benign ones the average age incidence is also slightly higher and growth is more rapid

Pathology

The gross anatomy of these tumours is largely determined by their mode of origin The growths invade the gland in which they arise and in the case of the parotid they may spread directly to the mandible the skull base of the brain and the skin Metastases are much less widespread than in most types of malignant disease The regional glands are involved in 15–20 per cent of the cases the lungs and pleura are the common sites of visceral deposits but the osseous system is rarely involved Metastases may show a tendency to encapsulation

Malignant tumours may be of the mixed tumour type basal-celled papillary cystic adenocarcinomatous or of squamous celled type

Secondary carcinoma may occur in any of the salivary glands Primary lympho sarcomas or fibro sarcomas occur and they behave as typical sarcomas

Clinical features

Growth is usually much more rapid than in the case of innocent tumours and pain is the outstanding feature The tumours often cause facial palsy and less often deafness and interference with the movements of the jaw The growths are usually hard in consistency encapsulated or ill defined and multiple masses may be present (Fig 22 (*a*) and (*b*)) The other physical signs include some degree of fixation to the skin and deeper tissues involvement of the seventh nerve possibly ulceration and local or other metastases It may be difficult to distinguish between a deeply situated innocent tumour which is wedged between the mastoid process the *mandible* and the external ear and a malignant tumour with early local invasion

REFERENCES

Blair V P and Padgett E C (1923) *Arch Surg Chicago* 7 1
Carmichael R Davie T B and Stewart M J (1935) *J Path Bact* 40 601
Chargin L and Rosenthal T (1931) *Arch Derm Syph Chicago* 24 236
Conway H (1938) *Surg Gynec Obstet* 66 1074
Cope V Z (1919) *Brit J Surg* 7 130
Fitzwilliam D C L (1927) *Brit J Surg* 14 472
Ford F R and Woodhall B (1938) *Arch Surg Chicago* 36 480
Fraser A (1918) *Surg Gynec Obstet* 27 19
Frey Lucie (1923) *Rev neurol* 2 97
Fridberg D (1931) *Dtsch Z Nervenheilk* 121 225
Fry R M (1927) *Brit J Surg* 15 291
Hart J T and White C (1934) *Illinois med J* 65 355
Harvey W F Dawson E K and Innes J R M (1938) *Edinb med J* 45 275
Hodges F M (1935) *South med J Nashville* 28 205
Horbst L (1931) *Z Hals- Nas - und Ohrenheilk* 30 151
Houck J W (1939) *Surgery* 6 550
Hybbinette S (1935) *Acta Chir Scand* 77 19
Ivy R H and Curtis L (1936) *Int J Orthod* 22 179
Kaminsky S D (1929) *Dtsch Z Nervenheilk* 109 296
Lemaitre F and Baudouin E (1934) *Ann Oto Laryngol* p 774
Lilienthal H (1917) *Amer J Surg* 31 101
McFarland J (1926) *Amer J Med Sci* 172 804
— (1936) *Surg Gynec Obstet* 63 457
McKnight H A (1939) *Amer J Surg* 45 128
New G B and Harper F R (1931) *Surg Gynec Obstet* 53 456
Norrish R E (1935) *Brit J Surg* 23 188
Patey D H (1940) *Brit J Surg* 28 29
Payne R T (1931) *Brit J Surg* 19 142
— (1931) *Brit J Surg* 19 142
— (1933) *Lancet* 1 348
— (1936) *Ibid* 1 655
— (1936) *Practitioner* 136 735
— (1937) *Lancet* 1 867
— (1938) *Proc R Soc Med* 31 398
— (1940) *Brit med J* 1 287
— (1940) *Lancet* 1 634
— (1944) *Brit J Radiol* 17 3
Pearson R S B (1935) *Arch Dis Childh* 10 363
Reischauer F (1931) *Ergebn Chir Orthop* 24 1
Rolleston J D (1938) *British Encyclopaedia of Medical Practice* Vol 9 London Butterworth
Rolleston H D and Oliver M W B (1909) *Brit med J* 1 1296
Schaffer A J and Jacobsen A W (1927) *Amer J Dis Child* 34 327
Schmieden V and Voss O (1931) *Dtsch Z Chir* 234 313
Seifert E (1926) *Dtsch Z Chir* 198 387
Smith M K (1939) *Ann Surg* 59 551
Stones H H (1948) *Oral and Dental Diseases* Edinburgh Livingstone
Trioumphoff A (1926) *Pr med* 34 1350
Vaughan W T (1925) *J Amer med Ass* 84 583
Werthin A S (1929) *J Cancer Res* 13 116
Wilson C W (1936) *Clin Sci* 2 273
Wood F C (1904) *Ann Surg* 39 57 207

Operative technique

The exposure of parotid tumours must always be adequate The technique to be followed must then depend on the size of the tumour and its relationship to its surroundings Sharp dissection through the adjacent parotid is often possible but blunt dissection should never be used Partial excision of the parotid has been increasingly advocated both for encapsulated tumours and for malignant ones after preliminary ligation of the external carotid artery Total parotidectomy should be reserved for obviously malignant cases Submaxillary tumours must be excised with the adjacent gland while the palatal ones are best treated by diathermy excision General principles of treatment must govern the removal of tumours in less common situations

Scheme of treatment

The following is a suggested scheme of treatment for the various types of cases likely to be met with but it deals primarily with parotid growths It must be remembered that the real value of pre operative and post operative irradiation of benign tumours is doubtful or negligible

1 Small and mobile
   Preliminary irradiation
   Excision
2 Large and mobile
   Preliminary irradiation
   Excision
   Post operative irradiation
3 Small and fixed
   Irradiation
   Operation if tumour becomes operable probably radical in type
4 Large and fixed
   Irradiation
5 Recurrent tumours
   On the lines of the above treatment of primary tumours

Post operative complications

These include facial nerve palsy salivary fistulae the auriculo temporal syndrome and recurrence Facial palsy is almost inevitable in a proportion of parotid cases and Ahlbom (1936) gives its incidence as 11 per cent in benign tumours Fistulae only occur after operation on the parotid and they are glandular in type and usually heal readily

REFERENCES

Ahlbom H E (1935) *Acta Radiol Suppl* 23
Apfeld G (1933) *Z Hals- Nas- -und Ohrenheilk* 35 152
Bassoe P (1932) *Med Clin N Amer* 16 405
Beck A L (1947) *Ann Otol &c St Louis* 56 439 722
Benedict E B and Meigs J V (1930) *Surg Gynec Obst* 51 626
Berard L Creyssel J and Colson P (1930) *Lyon Chir* 27 285
Blady J V and Hocker A F (1938) *Surg Gynec Obstet* 67 777

end but all these different varieties are of unimportance compared with congenital atresia with tracheo-oesophageal fistula of the type described The condition was first described by Gibson Physician General to the Army and a grandson of Oliver Cromwell in 1697 and an even earlier reference was made by Durston The anomaly was accurately described by Keith in 1910 and by a number of authors subsequently No attempt was made to treat the condition for a very long

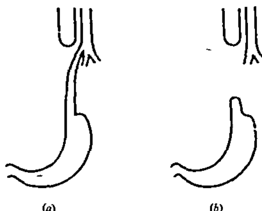


FIG 23 —(a) Commonest type of congenital oesophageal atresia upper oesophageal segment ends blindly at level of vena azygos arch lower segment arises from trachea (b) Second commonest type of congenital oesophageal atresia both segments end blindly there being no fistula Gap between segments may be large (*By courtesy of Lancet*)

time because it was thought to be extremely rare and it was also considered that any attempt at operative repair would be impracticable and in addition there was a fear that other equally serious anomalies were likely to be present If an attempt was made to treat the condition it usually consisted in carrying out a gastrostomy which was doomed to failure because it took no account of the regurgitation which took place from the stomach into the bronchial tree which invariably proved fatal

With a realization that the condition was not so uncommon as had hitherto been considered and moreover that many infants with this anomaly are quite healthy in every other respect further attempts were made to relieve the condition The first successful operation was one carried out in stages by Ladd in 1939 and again by Leven in 1950 The underlying principle of this operation was to bring the stomach to the surface and make an opening in it rather on the same principle as a colostomy with a spur and then to feed the infant through the lower opening and drain the secretions of the bronchial tree from the upper opening The disadvantage of these procedures was that for a very long time the child was faced with the prospect of undergoing a series of operations to reconstitute the oesophagus Realizing this disadvantage various surgeons attempted primary

CHAPTER 6

DEVELOPMENTAL ERRORS OF THE ALIMENTARY TRACT

R H FRANKLIN

DEVELOPMENTAL anomalies of the alimentary tract account for a number of deaths in the new born and during the early months of life In some instances the nature or the number of the deformities makes surgical treatment impossible but in others early diagnosis and the application of the proper treatment will result in the correction of the defect It must be remembered that many infants die as the result of one deformity although they are perfectly healthy and well formed in every other respect In order to lessen this wastage of infantile life it is essential *that every new born child should not only be examined for the more obvious* external deformities such as hare lip ectopia of the bladder imperforate anus or club feet but a careful watch must be kept for any untoward symptoms or signs which may arise The occurrence of these symptoms or signs is often noted accurately but unfortunately their significance may be improperly understood

The first essential is to possess a clear understanding of the deformities which may be encountered

The alimentary tract is the site of a variety of developmental errors which include re duplication atresia and stenosis and the anomalies of rotation Errors of re duplication may be manifest as an extra tube lying alongside the alimentary tract or may present as a cyst or diverticulum The importance of these various anomalies at different sites is discussed below

OESOPHAGUS

The most important congenital lesion of the gullet is congenital atresia in which there is a complete interruption in continuity There are several varieties of atresia of the oesophagus but the most common is that in which the upper oesophageal segment ends in a blind sac about the level of the vena azygos arch and the lower oesophageal segment springs from the back of the trachea by means of a fistulous communication near its bifurcation

Eighty per cent of all cases of oesophageal atresia fall into this category which is known as type IIIB according to the classification which was made by Vogt in 1929 In most of the remaining cases the lower segment is also blind and may be of any length in some cases it is a mere protuberance just reaching into the lower part of the mediastinum and in other instances it may reach as far as the upper segment (Fig 23) The other varieties in which there is a fistula between the upper segment and the trachea or between both segments and the trachea are all extremely uncommon In very rare instances a fistula occurs without any atresia and in other very rare cases a congenital diverticulum may be present which communicates with the rest of the oesophagus by a narrow opening at its upper

It the symptoms described occur all mouth feeding must be stopped and a well lubricated rubber catheter passed through the mouth and down the oesophagus If it is arrested 10-12 centimetres from the alveolar margin the diagnosis of atresia is almost certain In carrying out this test care must be taken not to use too soft or fine a catheter lest it curl up in the sac and give an erroneous impression of passing down into the stomach Having carried out this simple test the diagnosis is confirmed radiologically and it is of the greatest importance that this radio logical examination is carried out in such a way that no contrast medium is allowed to enter the lungs The best way of doing this is to screen the infant and first of all make a careful inspection of the lungs and note any consolidation and then examine the stomach and intestines for the presence of air If air is present below an oesophageal atresia it shows that there is a fistula between the lower oesophageal segment and trachea The absence of air in these circumstances usually but not always indicates that no fistula is present A catheter is introduced into the upper segment and ½–1 cubic centimetre of iodized oil is introduced under direct ob servation The appearance of the blind segment is quite characteristic and it is watched for a few minutes to make sure that there is no fistula between the upper segment and the trachea (Figs 24 and 25) The iodized oil is then withdrawn

Subsequent management

Once the diagnosis has been made the most important points to insist on are first to keep the blind sac empty secondly to change the position of the child regularly so as to give each lung the chance of expanding and thirdly to administer antibiotics If dehydration is present it should be corrected by parenteral methods No attempts at feeding should be made Provided all these details are attended to there is no reason why the operation should not be delayed for a few hours until the infant is transferred to some centre where the necessary facilities for carrying out the surgical treatment are available

THE OPERATION

The first successes were all achieved by an extrapleural operation carried out through an incision placed on the right side of the thorax starting at the level of the second rib one centimetre from the spine and running downwards and curving obliquely outwards to end over the sixth rib More recent successes have been recorded by the transpleural route and at the present time it is difficult to say which operation will eventually prove to be the better The transpleural operations in the early stages were all liable to kill the child either because of the failure to correct the collapse of the lung or from subsequent leakage causing a fatal empyema These troubles may possibly be prevented by a greater understanding of anaesthesia in small infants including the use of controlled respiration and also on account of the help afforded by antibiotics The author favours the extra pleural operation carried out under general anaesthesia The infant is placed in the prone position over a rubber hot water bottle which is half filled with water just about body temperature The right shoulder is slightly elevated the skin incision is made according to the above description and part of the fifth rib is resected subperiosteally When the correct plane has been found the pleura is gently separated and the incision is enlarged by dividing the fourth third and

anastomosis and Lanman had in fact tried the operation in 1936 but without success Haight and Townsley in 1943 were able to report a completely successful operation of direct anastomosis between the upper and lower segments of the oesophagus This operation has been followed by a series of successes first of all in the United States of America and subsequently in many other countries the first successful cases outside the United States being those of the author in 1947

DIAGNOSIS

It must be recognized that persistent cyanosis with excess of mucus occurring in the new born infant is more commonly associated with this anomaly than with any other condition and this fact must be borne in mind by all those who have



FIG 24—Congenital atresia type IIIB showing the blind upper segment filled with Lipiodol and stomach and intestines distended with gas



FIG 25—Congenital atresia of the oesophagus type II The blind upper segment is seen filled with Lipiodol and no gas is present in the stomach or intestine

the care of the new born Many normal infants are cyanotic and have an excess of mucus but once they are aspirated the improvement is rapid and maintained If the symptoms recur the presence of this anomaly should be suspected The child suffering from atresia is often anxious for the feed and sucks strongly and is then overcome by spluttering and cyanosis and regurgitation of the feed These symptoms seldom escape notice but only too often they are attributed to other causes

Early radiological examination is essential in all cases of suspected obstruction in infants and the examination is best made with the child held in the erect position If this procedure is carried out in the case of duodenal atresia the air shadow is seen to terminate abruptly at the site of the obstruction If the condition is one of stenosis the radiological appearance of the gas shadow may be difficult to interpret and it may be necessary to use a little barium emulsion Malrotation of the intestine with volvulus may give rise to difficulties in differential diagnosis

Barium should not be used if the obstruction is at a lower level than the duodenum nor without first excluding the possibility of an oesophageal atresia

Atresia and stenosis of jejunum, ileum and colon

Most of the anomalies in this part of the intestine occur in the ileum the jejunum is less commonly affected and the colon least of all Multiple sites of obstruction are found in 15 per cent of cases

The symptoms vary according to the site of obstruction and it must be remembered that vomiting may not occur for several days The vomit first contains bile and may later be mixed with meconium Abdominal distension depends upon the level of the obstruction and it may be accompanied by a ladder pattern type of visible peristalsis Dilated veins may appear on the abdominal wall An attempt should be made to diagnose the presence of obstruction before the clinical picture is advanced and to this end early recourse should be made to radiological examination in the erect position This will reveal loops of intestine distended with gas and showing fluid levels but the site of obstruction may be difficult to determine

Malrotation of the intestines

In the early embryo the intestinal tract is a straight tube which by a process of elongation and rotation comes to occupy the position found at birth

The part of the gut which is concerned in producing the anomalies about to be described is the mid gut which extends from the duodeno jejunal flexure to the middle of the transverse colon

Fraz r and Robbins have divided the rotation of the mid gut into three stages

First stage

The primitive gut is a straight tube with a dorsal mesentery lying in the sagittal plane As the gut grows in length it herniates into the umbilical cord and at the same time rotates through an angle of 90 degrees in an anti clockwise direction This process takes place at about the eighth week of intra uterine life If rotation stops at this stage and the gut is present in the umbilicus at birth the condition is known as exomphalos It may contain one loop of bowel or it may include the whole alimentary tract as well as the liver spleen and pancreas The size of the exomphalos may be such as to make the return of its contents into the abdominal cavity quite impossible or it may result in such an increase in the intra abdominal pressure that diaphragmatic embarrassment is produced

second ribs with the intervening intercostal bundles The displacement of the pleura is continued with great care until the vena azygos arch comes into view The lower end of the upper blind segment is usually to be found just deep to the vena azygos arch A search is now made for the lower segment and it is sometimes difficult to find Care must be taken not to confuse the aorta with the lower segment When the lower part of the oesophagus has been identified its fistula with the trachea is exposed and carefully ligated and divided To carry this out it is often necessary *to divide the vena azygos arch* but in many cases it has been found possible to expose all the necessary structures without dividing this vein and if it can be done *it is an advantage The two oesophageal* segments are *held* with stay sutures in order to avoid unnecessary handling The suture material used is No 5/0 silk carried on very small round bodied eyeless needles The sutures are lubricated with sterile liquid paraffin before use If anastomosis is feasible an opening is made in the blind upper segment and 3–4 interrupted sutures are introduced *on what will be the deeper part of the anastomosis It is important to include* mucous membrane in these stitches and it is important also to tie them just tight enough to approximate the parts without strangulating the intervening tissue When the posterior part of the anastomosis has been completed in this way a sterile rubber catheter is passed from the operation site down the oesophagus into the stomach and the other end is passed upwards into the pharynx where it is recovered and brought out through the mouth At this juncture it is a good plan to aspirate the air from the stomach The presence of the tube makes the com pletion of the anastomosis very much easier and when this has been carried out the tube is gently withdrawn The whole area is dusted with penicillin powder the lung is fully expanded and a little drainage tube left in the extrapleural space and connected with a water seal drain The rest of the wound is then closed in a water tight manner

After treatment

The infant is nursed in an oxygen tent to start with and care is taken to aspirate the nasopharynx during the first few hours The administration of antibiotics is continued and any dehydration is corrected Occasionally a blood transfusion may be required Twelve hours after the operation small feeds of penicillin solution are given by the mouth and if progress is satisfactory feeds of expressed breast milk are started In some cases leakage occurs at the site of anastomosis and if this leakage is considerable a temporary gastrostomy is required

INTESTINES

Duodenal atresia and stenosis

The symptoms and signs are those of a high obstruction Vomiting usually begins on the first dav and persists until the condition is relieved or death intervenes

The blockage usually occurs below the ampulla with the result that bile is found in the vomitus and is absent from the stools which are grey in colour The presence of bile or vomit in the stomach distinguishes the condition from congenital pyloric stenosis Those patients in whom *the obstruction is above the ampulla* pass normal meconium In a normal infant air reaches the sigmoid colon in 10 hours and this fact is of the greatest value in confirming the diagnosis of atresia

Early radiological examination is essential in all cases of suspected obstruction in infants and the examination is best made with the child held in the erect position If this procedure is carried out in the case of duodenal atresia the air shadow is seen to terminate abruptly at the site of the obstruction If the condition is one of stenosis the radiological appearance of the gas shadow may be difficult to interpret and it may be necessary to use a little barium emulsion Malrotation of the intestine with volvulus may give rise to difficulties in differential diagnosis

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Second stage

The mid gut returns to the abdominal cavity and at the same time rotates through 180 degrees in an anti clockwise direction This rotation takes place at about the tenth week of intra uterine life and it is thought that the proximal limb of the pre arterial segment re enters the abdominal cavity first passing beneath the superior mesenteric vessels and the mesentery The loops collect on the left side of the abdomen and as they do so displace the hind gut and its mesentery to the left The caecum and ascending colon return last and as they re enter the abdomen they are displaced to the right and turn through an angle of 180 degrees in an anti clockwise direction The duodenum in this way comes to occupy a position behind the superior mesenteric vessels while the colon lies in front Various anomalies may occur during this stage



FIG 26—Skiagram showing complete blockage of the barium swallow in the third part of the duodenum Blockage is due to a volvulus of the mid gut The use of barium is permissible in cases of high obstruction provided that tracheo-oesophageal fistula has been excluded but it should not be used for obstructions occurring lower down in the alimentary tract in infants

Non rotation—The mid gut re enters the abdomen in a horizontal plane with the result that the right side of the abdominal cavity is occupied entirely by small bowel while the colon and caecum lie on the left side The most important effect of this anomaly is to produce difficulties in diagnosis should the patient subsequently suffer from acute appendicitis

Mid gut volvulus—This may involve the whole of the mid gut from the duodeno jejunal flexure to the middle of the transverse colon or it may involve the small intestine only

The symptoms which are produced are usually those of recurrent duodenal

obstruction starting at birth (Fig 26) Occasionally there are no symptoms until a tight volvulus with strangulation occurs It is not usually possible to make a differential diagnosis before operation between a mid gut volvulus or a duodenal obstruction from other causes Early radiological examination is essential to confirm the diagnosis of small bowel obstruction

Malrotation and errors of fixation—The normal fixation of the mesentery from the duodeno-jejunal flexure to the right iliac fossa may not occur or bowel may be imprisoned beneath the mesentery during the process The lumen of the bowel may be obstructed at any level as the result of abnormal fixation and this is particularly liable to occur in association with the duodenum

The obstructive symptoms which are produced are extremely variable

The occurrence of various types of internal hernia can be explained on the basis of errors in fixation of the mesentery

Third stage

The caecum descends from its position just below the right lobe of the liver to its final position in the right iliac fossa An undescended caecum a retrocaecal appendix or a mobile caecum may result if the process is not concluded satisfactorily The presence of a mobile caecum may result in volvulus of the caecum

THE DIAGNOSIS AND TREATMENT OF INTESTINAL OBSTRUCTION DUE TO CONGENITAL ANOMALIES

The symptoms and signs of obstruction in the infant depend upon the level of the lesion whether it is complete or incomplete and whether it is associated with strangulation In all these respects the infant is comparable with the older patient The infant however is handicapped by not being able to complain of pain or nausea and it is an unfortunate fact that a degree of obstruction may be reached which is only rarely met with in an adult patient This state of affairs can be accounted for partly by unfamiliarity with the nature of the organic obstruction which may be present and partly by a natural reluctance to subject such a young patient to the hazards of an abdominal operation

The hazards of the operation have been reduced considerably by improvements in the surgical management and above all by earlier diagnosis and the risk of inflicting an unnecessary operation on an infant has been almost abolished by the use of radiological examination

Persistent or recurrent vomiting or distension should always raise the suspicion of intestinal obstruction until this diagnosis has been excluded A digital examination should be made if meconium has not been passed to make sure that the anus is patent

Pyloric obstruction can usually be distinguished by the absence of bile in the stomach and by the presence of reverse peristalsis

Radiological examination should be carried out as soon as there is any suspicion of obstruction The child is held in the erect position when distended loops of bowel showing fluid levels will be seen if obstruction is present It is usually impossible to diagnose the precise nature of the obstruction but some idea of its level is obtained in this way

The use of barium is undesirable

Second stage

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sutures of fine silk mounted on a fine round bodied eyeless needle The loops of bowel are steadied with these interrupted sutures while the posterior part of a continuous silk Lembert stitch is introduced

An incision about ½ inch long is made in each segment and a continuous silk *stitch which passes through all layers is carried right round the anastomosis* The Lembert suture is now completed All suturing must be carried out meticulously and care should be taken not to take too large a bite for fear of reducing the lumen

Post operative care

The stomach is kept empty by aspiration and the same attention is paid to hydration as before operation Feeding may be started on the third day The administration of antibiotics is continued

THE TREATMENT OF EXOMPHALOS OR AMNIOTIC HERNIA

If the hernia is very large it may be impossible to return the contents into the abdomen and in cases where it is possible it may be undesirable to do so because of the ill effects produced on the diaphragm by the increased intra abdominal pressure Gross has suggested a procedure in which the skin around the hernia is mobilized and used to cover the amniotic membrane which is left intact

An alternative procedure is to apply dressings of absolute alcohol with the object of hardening the amniotic membrane If this method is adopted it is essential to maintain the most scrupulous asepsis and to make full use of antibiotics

Whichever of these two methods is used a second operation is carried out 6 12 months later to approximate the muscles over the hernia Trouble may arise from sepsis or from obstruction occurring which necessitates an operation under unfavourable conditions but in spite of these disadvantages the two stage or delayed operation is the method to be recommended when faced with a large exomphalos The small exomphalos is conveniently dealt with by early operation

IMPERFORATE ANUS

All new born infants should be and usually are examined to see if the anal region appears normal What is not generally recognized is that the presence of an anal anomaly should lead to a careful examination to exclude any other abnormality This examination should include the passage of a soft rubber catheter into the stomach to make sure that the oesophagus is normal

One of the author s successful cases of congenital atresia of the oesophagus was diagnosed in this way The infant in question was a female and it was noticed that the anal dimple was absent and that meconium was emerging from a small opening on the posterior vaginal wall D C Perry was called to see the patient and bearing in mind the possibility of multiple anomalies he passed a catheter down the oesophagus and found that it was arrested 10 centimetres from the anterior alveolar margin *He made a provisional diagnosis* of oesophageal atresia and transferred the infant to my care Radiological confirmation was obtained and I

Meconium ileus

Meconium ileus may give rise to difficulties in diagnosis In this condition the meconium is abnormally thick and viscid as the result of pancreatic deficiency which in turn is due to fibrocystic disease of the pancreas

Obstruction from this cause usually occurs near the terminal ileum Radiologically there is a characteristic mottled appearance of the intestines without the abrupt termination of the gas pattern which is seen in volvulus or atresia

Pre operative management

Dehydration is corrected and the stomach kept empty by aspiration Antibiotics are administered

OPERATION

General anaesthesia is administered A vertical incision separating the fibres of the right rectus muscle is convenient and the incision must be sufficiently long to facilitate a proper exploration

The distended loops of bowel are allowed to escape from the wound and are covered with saline packs If the underlying cause is a mid gut volvulus the whole of the small bowel is distended and if the surgeon is not familiar with the condition the cause of the obstruction may easily be missed If all the intestines are allowed to extrude the twisted root of the mesentery can be palpated and the volvulus corrected Adhesions between the adjoining parts of bowel and mysentery must be separated and bands passing in front of the duodenum must be freed in a similar manner Unless these details are attended to the obstruction may not be relieved or the volvulus may recur In separating the adhesions care must be taken not to damage the engorged mesenteric veins

The bowel is returned to the abdomen in the non rotated position with the duodenum descending on the right side

If the cause of the obstruction is found to be duodenal atresia the most satisfactory procedure is duodeno jejunostomy but in cases where this is not practicable a gastro jejunostomy should be carried out

In cases of ileal or jejunal obstruction the point at which atresia or stenosis occurs can be found quickly after the distended loops have been allowed to escape from the wound The collapsed bowel below the obstruction is followed down to see if there are other atretic segments *this examination is facilitated* by injecting saline into the collapsed loop by means of a fine hypodermic needle This procedure also helps when the time comes to carry out the anastomosis between the collapsed and distended segments There may be several points of atresia with normal bowel in between and if the length involved is not excessive the best plan is to short circuit the whole affected segment It is alleged that the intervening normal segment will subsequently enlarge and require excision but it seems justifiable to risk this occurring and to deal with the problem later should it arise

Before making the anastomosis the distended loop should be emptied by means of a needle and syringe It is best not to use clamps The two selected segments of intestine are laid side by side and attached to one another by three interrupted

REFERENCES

Mackenzie M (1884) *Diseases of the throat and nose* Vol II London Churchill
O Reilly N Franklin R H and Daley M D (1944) *Arch Dis Child* 19 131
Plass E D (1919) *Johns Hopk Hosp Rep* 18 258
Potts W J (1947) *Surg Gynec Obstet* 85 14
Richter H M (1913) *Surg Gynec Obstet* 17 397
Singleton A C and Knight M D (1944) *Ann Surg* 119 556
Vogt E C (1929) *Amer J Roentgenol* 22 463
Webb J R D (1950) Two Cases of Duplication of the Alimentary Canal *Proc R Soc Med* 43 8 613

was able to operate on the child 12 hours after birth and before any injurious attempts at feeding had been made

If no other anomaly can be found attention should be directed to the anal condition but a careful watch must be kept for any signs of intestinal obstruction If the anal defect is in the nature of a thin septum it should be divided carefully and subsequently kept dilated A recto vaginal fistula is best treated by dilatation until the child is big enough for reconstructive surgery to be undertaken If dilatation proves difficult it may be wise to make a colostomy in the hope that the normal arrangement can subsequently be restored

The management of patients in whom there is no anal dimple or fistula is difficult It is sometimes possible to see how much of the bowel is deficient by making a radiological examination with the child held vertically head downwards and with a metal marker on the perineum The distance between the gas bubble and the perineum may be small enough to justify a cautious perineal exploration If this is done an assistant should press gently on the abdomen in order to bring the distended rectum down towards the surface If the rectum can be reached easily in this way it is opened and attached to the skin wound by four interrupted sutures The objection is sometimes raised that this procedure leaves the patient with an incontinent perineal anus and that it is less distressing to be provided with a colostomy which can be properly supervised On the other hand a number of patients who do not appear to have any strong anal musculature are able to remain continent provided that the bowels are kept regular

Nothing is lost however by a fair trial and a colostomy may be resorted to later should it prove necessary

If the deficiency in the rectum is considerable a colostomy should be carried out without delay

REFERENCES

Brenneman J (1918) *Amer J Dis Child* **16** 143
Franklin R H (1947) *Lancet* **2** 243
— (1948) *Ann R Coll Surg Engl* **2** 69
Frazer E and Robbins R H (1915) *J Anat Paris* **50** 75
Gage M and Ochsner A (1936) *Ann Surg* **103** 725
Gamble H A (1938) *Ibid* **107** 701
Gardner C E (1950) *Ibid* **131** 6 879
Gibson T (1697) *The Anatomy of humane bodies epitomi ed* p 239 5th ed London
Grey Turner G (1946) *Injuries and Diseases of the Oesophagus* London Cassell
Grove L and Rasmussen E (1950) *Ann Surg* **131** 6 869
Guthrie K J (1945) *J Path Bact* **57** 367
Haight C (1944) *Trans Amer Surg Ass* **62** 623
— (1944) *Ann Surg* **120** 623
— and Townsley H A (1943) *Surg Gynec Obstet* **76** 672
Holt F J Haight C and Hodges F J (1946) *Radiology* **47** 457
Humphreys G H (1944) *Surgery* **15** 801
Keith A (1910) *Brit med J* **1** 301
Ladd W E (1944) *New Eng J Med* **230** 625
Lanman T H (1940) *Arch Surg* **41** 1060
Leven N L (1939) *J Thoracic Surg* **9** 213
— (1941) *Ibid* **10** 648

congenital short oesophagus the surgeon who examines the organ rarely finds any true congenital shortening Again the abdominal and thoracic surgeons approaching the hiatus from different aspects have expressed quite different views on the fundamental pathology of the abnormality and its causation

The pattern of specialization in medicine is changing and the trend for it to be based upon anatomical regions rather than specific methods of diagnosis and treatment has led to the functions of physician surgeon endoscopist and to a lesser extent those of the radiologist being vested in the same clinician As a direct result of this a much clearer and more complete picture of this condition is emerging The surgeon who performs his own oesophagoscopies is in a position to appreciate not only the incidence and importance of reflux oesophagitis and fibrous stenosis as complications of hiatus hernia but also the normal and abnormal physiology of the cardia and the fundamental aberration accompanying hiatus hernia for example the patulous cardia which is responsible for most of its complications Tribute must here be paid to the work of Allison whose several papers on this subject have contributed so much to our present concept of the underlying pathology and the rationale of its correction Much of this review is based upon the results of Allison s investigations

Incidence

The recent and dramatic increase in the frequency of diagnosis of hiatus hernia is the result of improvements in radiological technique Soresi (1919) first described the head low position for the reflux filling and delineation of the cardia and lower oesophagus but not till the last 2–3 years has this manoeuvre been generally adopted by radiologists as a routine procedure without which no examination of the oesophagus and stomach is complete Few hiatus hernias can be demonstrated by the barium swallow with the patient erect few will escape detection by the Soresi manoeuvre and its modifications

The Mayo Clinic figures quoted by Guthrie and Jones (1940) are illuminating In 1908 a hiatus hernia was first found at operation and in 1921 the first radiological diagnosis was made Between 1908 and 1926 the diagnosis was made 17 times between 1926 and 1938 399 cases were diagnosed

In 1948 Allison published observations based upon 63 cases in his most recent publication (1951) this figure has risen to 204 Ninety four proven cases have been admitted to Frenchay Hospital 9 between 1944 and 1947 and 85 since 1947 At most clinics a sufficient number of cases have been fully investigated to lead to general agreement that hiatus hernia is probably one of the commonest pathological conditions assailing the upper intestinal tract

By contrast the number discovered on routine autopsy examination is negligible Undoubtedly the eviscerating technique adopted by the morbid anatomists so distorts the anatomical relationship of the cardia to the diaphragm that even gross abnormalities in this region can and do escape detection Moreover the external appearance of the herniated portion of the stomach may bear such a close resemblance to the normal oesophagus that it is not recognized as such Thirdly the dramatic angry changes that confront the oesophagoscopist in the presence of reflux oesophagitis pale into insignificance in the autopsy specimen Non malignant strictures in the lower oesophagus when discovered have been erroneously

CHAPTER 7

DIAPHRAGMATIC HERNIA

RONALD BELSEY

INTRODUCTION

DIAPHRAGMATIC hernias have been variously classified in the past usually into the congenital and acquired with the latter group subdivided into the traumatic and non traumatic

This classification has been out dated by a growing conviction that the hiatus hernia previously regarded as an acquired condition of the fifth to seventh decades may in fact be a congenital abnormality or the direct result of some developmental aberration of the crura of the diaphragm No useful purpose is served by attempts to simplify unduly the classification as the types encountered are few in number and the effects of the hernia are governed largely by the position and size of the defect in the diaphragm

In order of frequency these defects are

1 the abnormal oesophageal hiatus
2 the patent pleuro peritoneal canal or foramen of Bochdalek
3 the para sternal hiatus or foramen of Morgagni and
4 the defect of congenital absence of a part or the whole of one diaphragm

The traumatic hernia deserves separate consideration on several accounts (a) the defect can occur anywhere (b) associated lesions traumatic or inflammatory usually complicate the picture and (c) clinically this type threatens the greatest danger to the patient Many excellent descriptions of this type have appeared during recent years to which little can be added

The first two types only will be discussed in this chapter Recent observations have added much to our knowledge of hiatus hernia its complications and management and these will be reviewed advances in diagnostic and surgical technique that have improved the prognosis in the congenital pleuro peritoneal canal hernias of infancy will also be discussed

HIATUS HERNIA

Much has been written on this condition aptly called the masquerader of the abdomen but the views expressed regarding diagnosis prognosis and treatment vary within wide limits depending upon the clinician s approach the physician the surgeon the radiologist and the endoscopist have only recently met on common ground to pool their observations and correlate their deductions

For example Allison (1948) has stressed the frequency with which hiatus hernia is complicated by reflux oesophagitis and has drawn attention to its dangers Harrington (1948) mentions it only to dismiss it as having little bearing on prognosis and treatment The radiologists have long confused hiatus hernia with

based upon routine radiological examination of normal subjects by the Soresi technique Brick and Amory (1950) found 4 cases of hiatus hernia in 300 ambulatory male patients over the age of 50 years Sherman (1948) found cases of hiatus hernia of various types and degree in 1 576 patients over 45 years without gastro intestinal symptoms Rigler (1948) noted an appreciable number of hiatus hernias apparently symptomless while studying 544 symptomless persons over 50 years with achlorhydria or free hydrochloric acid of less than 30 units Shanks (1948) estimates that 20 per cent of cases are asymptomatic Only 4 of Wilkinson s (1934) 70 cases were free of symptoms that could be attributed to the hernia but Ritvo (1930) found 14 of 60 cases free from symptoms Ohler and Ritvo (1943) found only 9 out of 136 and Moersch (1938) 19 out of 246 patients symptom free On the other hand Radloff and King (1947) decided that in only 15 out of 50 cases could the predominant symptoms be attributed to the hernia St John Swenson and Harvey (1944) found 25 cases amongst 2 413 patients over 50 years with no digestive symptoms but most of the patients were examined in the erect position and so this figure is probably on the low side

The considerable variations in the figures quoted above can be explained by the different significance attached to certain symptoms by clinicians Brick (1949) in a recent study of 308 cases found concomitant lesions in 25 per cent of them In the past there has been a tendency to attribute to concomitant disease symptoms which are now regarded as typical of hiatus hernia and a study of the more recent papers leads to the conclusion that in relatively few cases is no distress to the patient caused by a hernia

Of the frequency of hiatus hernia as a cause of upper abdominal symptoms there is little doubt Brick (1949) found that in 3 448 patients undergoing radiological study of the upper gastro intestinal tract hiatus hernia was the second most frequent diagnosis duodenal ulcer was diagnosed in 705 patients and hiatus hernia in 308 or 8 93 per cent The incidence in patients with symptoms varies from 2 to 10 per cent of all barium examinations in series reported from different hospitals

The diagnosis is sometimes made on mass miniature radiography but as only antero posterior films are taken and as few hernias of this type are visible in straight skiagrams the figures have little significance Moreover the discovery by this means will depend largely on the ability of the radiologist who reads the miniature films to interpret cystic shadows in the mediastinum

Sex incidence

Here again there is no general agreement and the incidence in three of the larger series is given in Table I

TABLE I

	Cases	Male	Female
Brick – –	308	143	165
Harrington –	219	140	79
Allison – –	172	56	116

classified as congenital in origin and the underlying hernia missed If pathologists could be persuaded to examine at every autopsy the position of the oesophago gastric mucosal junction relative to the position of the hiatus many more hernias would come to light but it is doubtful if autopsy records will ever be of much value in assessing the incidence of a condition which is essentially a physiological rather than an anatomical abnormality of the lower oesophageal sphincter

One of the outstanding problems concerns the incidence of asymptomatic hernias It is well known that not every hiatus hernia gives rise to complications nor causes the patient to seek medical advice and relief The evidence available is



(a)

Fig 27—(a) Barium swallow with the patient erect revealing no evidence of a hernia (b) same patient radiologically examined in the head low position hiatus hernia well shown

(b)



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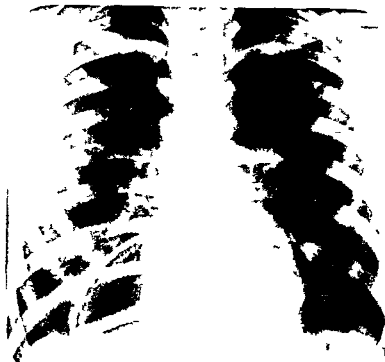
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(a)

FIG 28 —(a) Antero-posterior and (b) lateral skiagrams of a patient with a Type II hiatus hernia showing the typical cystic shadow projecting from the posterior mediastinum into the right pleural cavity



(b)

Age incidence

In Brick s series 76 per cent of the patients were in the 50–80 years age group and on this distribution there is general agreement The diagnosis is very infrequently made between the ages of 10–40 years It is now realized that the condition occurs in infancy and childhood and the diagnosis should be considered in every case of persistent vomiting haematemesis and anaemia in the neonatal period and childhood and the appropriate barium examination carried out Harrington found 5 children suffering from hiatus hernia in a series of 242 cases but in a series of 94 cases admitted to Frenchay Hospital 14 of the patients were children Findlay and Brown Kelly (1931) reported 9 cases in children mostly complicated by fibrous stenosis secondary to reflux oesophagitis When more children are investigated for this lesion so the incidence will probably increase The discovery of the fully established condition in early infancy—the youngest pati nt in the Frenchay series was an infant of 3 weeks—suggests that this type of hernia may be a true congenital abnormality The infrequ^ncv of the diagnosis in the se ond to fourth decades and the delay in the onset of symptoms till the sixth decade in the majority of cases has yet to be explained satisfactorily



FIG 29 —Barium swallow showing a hiatus hernia in an infant of 3 weeks with haematem sis and anaemia oesophagoscopy revealed reflux oesophagitis and ulceration of the mucosa

Pathology

This description is based upon the views so lucidly expressed by Allison views which offer the only rational and convincing explanation of the clinical effects of this abnormality

There is no intrinsic sphincter at the lower end of the oesophagus but an efficient extrinsic sphincter mechanism which in the normal person allows the passage of the food bolus from the oesophagus to the stomach but effectively

prevents the reflux of gastric contents in the opposite direction There are three distinct elements contributing to the sphincter

(a) the pinch cock action of those fibres of the right crus forming the margins of the oesophageal hiatus

(b) the sharp backward angulation of the lower end of the oesophagus caused by the contraction of the crura and

(c) the acute angle of entry of the oesophagus into the stomach at the cardia

Allison has likened the action of the fibres of the right crus on the oesophagus to those of the pubo rectalis on the rectum

The efficiency of this mechanism depends upon (a) the normal arrangement of the fibres of the right crus especially posteriorly where the muscular ring of the hiatus is weakest (b) the muscular tone and activity of these fibres and (c) the normal relationship of the cardia to the hiatus with the oesophago gastric mucosal junction lying wholly below the diaphragm

A hernial sac is always present and a recess of the peritoneal cavity projects upwards through the hiatus in front of the stomach The greater portion of the herniated stomach is not invested with peritoneum and the sac which is almost invariably empty appears to play little part in the pathology of this type of hernia

The phreno oesophageal ligament a condensation of the deep fascia on the under surface of the diaphragm passes up through the hiatus to blend with the fascia investing the oesophagus and assists in maintaining the position of the cardia within the hiatal ring during the descent of the diaphragm on inspiration During this phase of respiration the crura contract the pinch cock tightens increases the angulation of the diaphragmatic portion of the oesophagus and thus overcomes the greater tendency to reflux occasioned by the fall in the negative intrathoracic pressure and rise in intra abdominal pressure during inspiration

The most important element in the pathology of hiatus hernia is the physiological failure of the diaphragmatic pinch cock and the resulting reflux of acid gastric peptic secretion into the oesophagus ill equipped to withstand its erosive action The symptoms of hiatus hernia are largely those of its complications If there existed an efficient intrinsic sphincter at the cardia the position of *the cardia* relative to the hiatus would be of little moment

Some patients present all the typical symptoms of hiatus hernia and reflux oesophagitis may be seen on oesophagoscopy but no hernia can be adequately demonstrated radiologically At operation a deficient hiatus and patulous cardia are found but no herniation of the stomach above the diaphragm and none can be caused to slide by traction on the oesophagus Posterior repair of the hiatus in these cases can restore the diaphragmatic pinch cock and lead to prompt healing of the oesophageal mucosa with relief of symptoms

Whether the primary failure of the pinch-cock is due to a congenital deficiency of the right crus and the posterior margin of the hiatus or to a defect of the phreno oesophageal ligament is uncertain Allison favours the former view Harrington the latter The observations of *thoracic surgeons who repair these hernias from* above support the muscular theory Moreover the technique of posterior repair with reconstruction of the posterior margin of the hiatus has lowered the incidence of recurrence lending further support to the theory on which this method of treatment has been developed

The occurrence of herniation in early infancy supports the view that hiatus hernia should be regarded as congenital in origin based upon a developmental abnormality of the diaphragm Certain events occurring later in adult life such as the rise of intra abdominal pressure during the later months of pregnancy the accumulation of abdominal fat muscular degeneration and loss of tone may lead to further herniation and the onset of symptoms Rigler and Eneboe (1935) demonstrated a hiatus hernia on radiological examination in 18 per cent of 195 pregnant women in 3 out of 10 of these women who were examined again after delivery a hernia was still present

The development of the diaphragm has been variously described by numerous authors but it is obvious from these descriptions that much investigation has yet to be done by the embryologists before any lucid conception of the development especially of the crura emerges Till this development is better understood no further light can be thrown on the aetiology of hiatus hernia

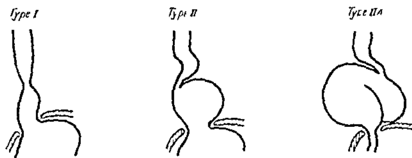


Fig 30 —Diagrams showing principal types of hiatus hernia encountered Types I and II correspond to Allison s sliding and rolling types respectively

Once the cardia has escaped into the thorax the further development of the hernia follows one of two main patterns Allison has designated these two main types as the sliding hernia and the rolling hernia terms which are self explanatory the latter corresponds to the para oesophageal type of other authors In the former the oesophagus enters the apex of the gastric pouch obtusely in the latter the cardia may be at any point below the apex and may remain at the level of the hiatus The essential difference between the two types lies in the angle of entry of the oesophagus into the stomach and in the rolling type this angle is acute In the sliding type the cardia is completely patulous but in the rolling type distension of the gastric pouch may render the angle of entry even more acute and may obstruct the lower oesophagus by pressure thus preventing any reflux of gastric contents This is borne out by clinical evidence the complications in the two types being different Reflux oesophagitis so common in the sliding type is rare in the rolling type

The classification has been unduly simplified for descriptive purposes In practice every gradation between the two types is seen and Allison has described cases in which elements of both types are seen in the same case





FIG. 31.—Barium studies of the various types. (*a*) Type I hernia with completely patulous cardia. (*b*) Type II hernia with obstruction of lower oesophagus by pressure.

FIG 31 (*contd*)—(*c*) Type II variant— para-oesophageal hernia (*d*) Type IIa nearly the entire stomach lies above the diaphragm and the pylorous is obstructed at the hiatus



(c)



(d)

In the absence of more exact information on the mode of evolution of these hernias such terms as sliding and rolling are undesirable and at Frenchay Hospital a noncommittal classification has been adopted (Fig 30) Type IIA in which the greater portion of the stomach has herniated into the thorax is merely a further development of Type II corresponding to Allison s rolling type This classification is justified by the difference in complications that occur in the two types and is of some clinical value in indicating prognosis In general the larger the herniated portion of the stomach the fewer are the symptoms

The incidence of the two main types of hernia and their combinations in Allison s 205 cases is given in Table II

TABLE II

Incidence of Two Main Types of Hernia—Allison

170	sliding
6	sliding and rolling
21	rolling
7	rolling and sliding
1	congenital short oesophagus
205	(2 sliding recurrences following repair of rolling hernias)

94 CASES—FRENCHAY

Type I - - -	70
Types II and IIA -	24
	94

The radiologists have contributed much to our knowledge of this condition but they have also contributed views on its pathology which are hardly justified by the evidence limited to radiological appearances which they produce in support of these views First there is the conception of the sliding hernia that can appear or disappear with changes in the position of the patient The bolus of barium can be seen to slide above and below the level of the hiatus on screening but this does not justify the inference that the herniated portion of the stomach automatically follows suit The oesophagus is a powerful muscular tube and the retraction caused by tonic contraction of its longitudinal muscle fibres when the cardia escapes the fetters of its normal ligamentous attachments to the margins of the hiatus is assuredly enough to resist the action of gravity Any surgeon who has divided the oesophagus and observed the upper end to retract almost out of sight into the superior mediastinum can vouch for the muscular tone of the organ The direct evidence obtained at thoracotomy does not suggest that many of these hernias can slide to and fro The author in a series of 80 cases operated upon personally by the thoracic route has found in the great majority sufficient adhesions between the lower oesophagus and stomach and the surrounding mediastinal structures to effectively prevent the herniated stomach being either pushed down from above or dragged down from below till it has been freed from its attachments

The second view over which the radiologists can be taken to task concerns the conception of the congenital short oesophagus a term applied by them to the Type I hernia for many years past They have fallen into the error of assuming that because the oesophagus looks short it is short Nothing could be further from

the truth The living oesophagus when freed from its upper and lower attachments can probably retract to half its normal length and when retraction from below upwards is permitted by the presence of a hiatus hernia this should not be called congenital shortening It is suggested that the diagnosis of congenital short oesophagus should never be made except at operation when the muscular retraction can be overcome and the length of the organ relative to the adjacent structures can be actually measured

The condition of true congenital shortening does occur as demonstrated in Barnard s case quoted by Barrett (1950) but it is very rare compared to hiatus hernia with muscular retraction Allison has reported only one instance of true congenital shortening among 204 cases of hiatus hernia Shortening due to fibrosis



FIG 32.—Barium swallow showing congenital short oesophagus at operation the shortening was found to be apparent only and the hernia was completely reduced without difficulty

of the lower third of the oesophagus associated with some degree of stenosis frequently complicates chronic reflux oesophagitis but as Allison has stressed this is essentially acquired shortening and not congenital in origin In the Frenchay Hospital series of 94 cases there were 33 instances of acquired shortening associated with varying degrees of stenosis and chronic reflux oesophagitis but there was not a single instance of true shortening in the absence of active or healed oesophagitis Harrington found at operation that in some of the cases diagnosed by Moersch as having short oesophagi there was no true shortening in actual fact

The concept of congenital shortening has retarded progress in this field and also the evolution of satisfactory methods of treatment by discouraging surgeons

from attempting to undertake surgical repair in cases in which it is now realized that repair is possible and can lead to complete relief from symptoms

Just how misleading radiological appearances can be is demonstrated by the case illustrated in Fig 32 A diagnosis of congenital short oesophagus had been made but exploratory thoracotomy revealed no true shortening and complete reduction and repair was performed without difficulty

It has been shown by several experimental workers that vagal stimulation in the animal can lead to retraction of the oesophagus and herniation of the cardia above the diaphragm Concomitant abdominal disease is frequently present in association with hiatus hernia—in 25 per cent in Brick s series—and Smithers (1950) has suggested that these co existing lesions in the gastro intestinal and biliary tracts

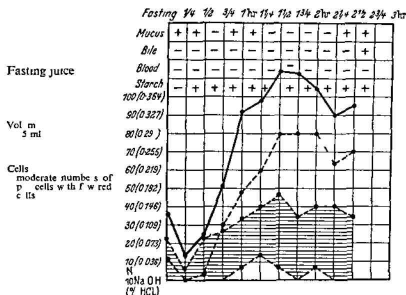


FIG 33—Typical high climbing acid curve in patient with a hiatus hernia

cause persistent vagal stimulation and reflex retraction of the oesophagus and may therefore be the cause of the hernia Further evidence is necessary before this theory regarding the aetiology can be accepted Other abdominal lesions amenable to clinical diagnosis are not found in the majority of cases

Andersen (1949) has investigated the influence of hereditary factors in the aetiology of hiatus hernia and has found that by subjecting young rat to vitamin A deficiency hiatus hernia can frequently be produced in hereditarily susceptible strains

Gilbert Dey and Rall (1946) and other American authors stress the importance of emotional factors in the causation of the condition and probably subscribe to the vagal stimulation theory The symptoms of the uncomplicated hernia are essentially intermittent and unpredictable in their occurrence and it is conceivable that in the patient who never knows when she may have to rush from the table to

regurgitate the emotional disturbance may be secondary to the hernia rather than the cause of it

Few investigations have as yet been undertaken to determine what if any changes occur in gastric function in the presence of a hiatus hernia In 52 of the Frenchay Hospital series fractional test meals were performed In 36 of these cases the acid curve was above normal dramatically so in many instances There were two characteristic patterns either a very high initial rise followed by a rapid fall or a steady climb throughout the period of the test The former pattern was seen more frequently In 9 cases the acid curve was within the normal range in 7 it was low and in 4 of these there was complete achlorhydria but there was some doubt as to whether the tube had entered the stomach Control fractional test meals on patients in the same age groups in hospital for other conditions showed acid curves within the accepted normal range Further studies are necessary before and after surgical repair before any conclusions can be drawn from these figures No fractional test meal results however are significant in an investigation of this kind unless repeated on several occasions and accompanied by radiological evidence of the presence of the tube within the stomach

Complications

Oesophagitis —The most important and one of the more frequent complications of hiatus hernia is reflux oesophagitis an acute superficial inflammation with ulceration and membrane formation occurring in the lower oesophagus as a result of the reflux of gastric contents through the patulous cardia This condition was formerly known as peptic ulceration of the oesophagus but as Barrett has pointed out this term is best reserved for a quite different condition namely chronic peptic ulceration of the herniated portion of the stomach

Allison first drew attention to the frequency of this complication and to its serious consequences for the patient In his series of 176 hiatus hernias of the sliding type reflux oesophagitis was present in 136 or 77 per cent In the Frenchay Hospital series this complication was encountered in 36 of 63 cases of Type I hiatus hernia in which oesophagoscopy was performed an incidence of 57 per cent In contrast to these figures the incidence in American series is very low and few authors comment on the condition or its sequelae Harrington noted the presence of ulceration in the lower third of the oesophagus but considered it to be traumatic in origin due to the to and fro movement of the oesophagus in the hiatus The reasons for the wide discrepancy in the reported incidence of this complication are fairly obvious In the first place thoracic surgeons in Great Britain are in the habit of performing their own oesophagoscopies and usually undertake this investigation in every case of hiatus hernia as a routine method of investigation in view of the frequency of dysphagia as a symptom of the condition In many clinics in America and elsewhere the oesophagoscope remains in the hands of the professional endoscopist By analogy it is not difficult to imagine what would have been the present state of urogenital surgery and our knowledge of bladder pathology had cystoscopy been claimed as the perquisite of the endoscopist Secondly many oesophagoscopes on the market are not long enough to reach the cardia and as the ulceration is frequently limited to the lower inch of oesophagus it may easily escape detection even when oesophagoscopy is said to have been performed In the third

place reflux oesophagitis and superficial ulceration cannot be revealed by radiological examination but can only be inferred when it has progressed to fibrous stenosis Fourthly when the inflammatory changes secondary to the reflux have been observed by the endoscopist they have not infrequently been misinterpreted as malignant in origin In few papers on hiatus hernia is *there any mention of* oesophagoscopy or its sinister revelations and Dunhill (1948) does not comment on this complication of reflux oesophagitis merely stating that Apart from one case in which a deep chronic ulcer was present ulceration has not been demonstrated either by radiological examination or at operation

Reflux oesophagitis occurs far more frequently as a complication of the sliding or Type I hernia than of the rolling or Type II variety and it is rarely associated with the latter type The acute angle of entry of the oesophagus into the stomach in the latter type may form a valve capable of resisting the reflux of gastric contents into the oesophagus In this type the intrathoracic stomach is usually more voluminous than in the sliding type and may be adequate to accommodate the gastric contents ejected from the intra abdominal part of the stomach during phases of increased intra abdominal pressure as during stooping and so act as a buffer between the stomach and the oesophagus The greater the portion of stomach lying above the diaphragm the more acute is the angle of entry likely to be

This purely anatomical explanation of the occurrence of reflux oesophagitis does not account for every case nor does it explain satisfactorily why certain patients with Type I hernias may quite suddenly develop this complication relatively late in life In the Frenchay Hospital series all but two of the patients with oesophagitis had abnormally high climbing acid curves

Diffuse mucosal inflammation occurs first at the cardia then spreading upwards to involve the lower third of the oesophagus but rarely is the middle third involved Superficial ulceration occurs first along the crests of the rugae but later involving the whole of the mucosa in this area The ulcers are covered with pale grey membrane which is easily detached from their surface The muscular layers are oedematous and there is marked hyperaemia of the peri oesophageal tissues

The inflammation may heal spontaneously at any time or under the influence of treatment Cases are seen at operation in which although oesophagoscopy reveals no evidence of active ulceration *the extent of the chronic peri oesophagitis and* the fibrous adhesions to the surrounding mediastinal structures suggest that there must have been severe inflammation of this organ at some time in the patient s life

The oesophagitis often becomes chronic The whole wall of the lower third becomes infiltrated with fibrous tissue secondary stenosis and shortening then occur The length of the stricture varies but the whole of this segment may become involved The ulceration and stenosis however suddenly end at the junction of the lower and middle thirds and very rarely is there any involvement of the latter segment Gravity may play some part in limiting the inflammation or the mucosa of the middle third may be more resistant to the erosive action of gastric secretion Following a normal act of swallowing as viewed on the x ray screen the residual column of barium occupies the lower third in the erect position and repeated swallowing may help to limit the action of regurgitated acid to the lower third any acid in the upper reaches may also be *more effectively buffered by the down*ward stream of saliva When the degree of stenosis becomes marked further

Fig 34.—Secondary stenosis (*a*) Child aged 1 year with chronic ulceration and fibrous stenosis of the lower third of the oesophagus (*b*) chronic ulceration *with secondary stenosis and shortening in a* woman of 59 years suspected of having a malignant stricture—serial sections of the stenosed segment resected at operation revealed no evidence of growth



(*a*)

(*b*)

regurgitation may be prevented mechanically but not before the stage of severe dysphagia has been reached

Microscopic examination of a portion of oesophageal wall from the ulcerated area reveals gross thickening of the wall and from within outwards complete destruction of the mucosa and replacement by granulation tissue infiltration of the submucosa by inflammatory cells infiltration of the muscle layer with fibrous tissue and fibrosis and hyperaemia in the peri oesophageal tissues

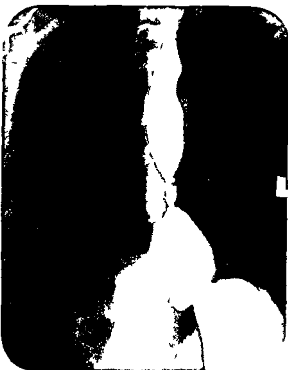


Fig 35 —Type I hernia complicated by chronic reflux oesophagitis and commencing stenosis at the cardia



Fig 36 —Barium swallow of a child aged 5 years with chronic ulceration and stenosis of the whole of the lower third of the oesophagus secondary to a hiatus hernia

Reflux oesophagitis leads to thickening of the oesophageal wall not penetration or perforation Penetrating ulcers have been seen by radiologists in the region of the cardia in cases of hiatus hernia but as Barrett has stressed these ulcers are true peptic ulcers acute or chronic of the herniated portion of the stomach and are not oesophageal ulcers at all Peptic ulceration of the intrathoracic stomach has the same pathology and may run the same course as peptic ulceration of the abdominal stomach The radiologists have been rather carried away by the idea of the chronic penetrating oesophageal ulcer and unmindful of the findings at oesophagoscopy and operation are wont to interpret every slight irregularity in the outline of the inflamed segment of the oesophagus as an ulcer crater frequently embellishing the skiagram with arrows to show its position Such confidence has proved rash as without the help of metal markers placed in position by the endoscopist the

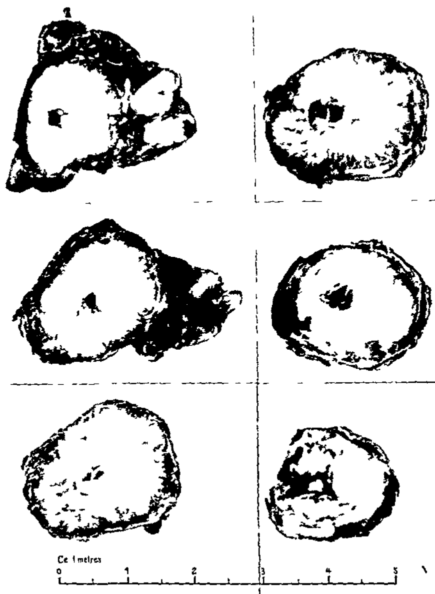


Fig 37 —Cross sections at different levels of the stenosed segment of oesophagus resected from the child illustrated in Fig 36 The mucosa has been completely destroyed and the segment is lined by granulation tissue only The degree of fibrosis and thickening of the wall suggests the futility of attempts at dilatation

oesophago gastric mucosal junction cannot be demonstrated by radiological examination

Areas of heterotopic gastric mucosa may occur in the wall of the oesophagus and in theory these areas may be the site of characteristic peptic ulceration The areas are usually very small and as Brown Kelly Schridde (1904) Taylor (1927) Rector and Connerley (1941) have pointed out are nearly always found in the upper third of the oesophagus and post cricoid region Barrett has stated that Nobody who has studied heterotopia of gastric mucosa in the oesophagus has described a pathological lesion in an isolated islet and thus nobody has certain evidence that ulceration has occurred in an islet

Until recently the assumption that the inflammatory changes seen in the lower third of the oesophagus are due to the erosive action of acid peptic gastric secretion has been based on clinical and endoscopic evidence Ferguson and Wangensteen and their associates (1950) have recently demonstrated that by perfusing the lower oesophagus of an experimental animal with gastric secretion all the pathological changes of reflux oesophagitis can be produced with dramatic rapidity up to the stage of complete destruction of the oesophageal wall and perforation Perfusion with acid alone in concentration similar to that occurring in gastric secretion produced only mild changes in the mucosa

One of Allison s greatest contributions to our knowledge of the condition has been to call attention to the high incidence of fibrous non malignant stenosis as a complication of the sliding type of hiatus hernia In his 176 cases of this type 23 per cent of the men and 57 per cent of the women were thus afflicted In discussing these cases Allison states In considering these statistics it must be remembered that a patient with oesophageal obstruction is more likely to be referred to a thoracic surgical department than one with flatulence and heartburn but an effort has been made to minimize this by considering only those patients seen in the last 5 years when the syndrome of sliding hernia has been more widely recognized in the hospital more carefully looked for in the radiological department and more often investigated by oesophagoscopy so that the figures probably come close to representing a cross section of modern general hospital practice

Intestinal obstruction —Hiatus hernia may be complicated by obstruction at three points (1) by fibrous stenosis of the lower third of the oesophagus (2) at the neck of the stomach where it passed through the hiatus and (3) at the pylorus or duodenum

Oesophageal stenosis has already been discussed

Obstruction at the hiatus is unlikely to occur in view of the widening of the hiatus that is present but radiological examination occasionally suggests a hold up in this position which may be responsible for the regurgitation of freshly ingested food soon after the commencement of a meal a common symptom

Obstruction at the pylorus or duodenum can occur in Type IIA hernia where the whole of the stomach lies above the diaphragm and the duodenum is dragged up through the hiatus and kinked round its sharp fibrous right margin in this type the bulk of the stomach usually herniates into the right side of the chest increasing the kinking of the duodenum In the 94 cases treated at Frenchay Hospital severe duodenal obstruction has been encountered in 3 all children under the age of 3

years Volvulus of the herniated stomach and strangulation are describ d by Dunhill but these complications are very uncommon

Haemorrhage—Haematemesis occurred in 18 p r cent of the Frenchay series but in no case was it severe In view of the readiness with which the ulcerated oesophagus bleeds on the slightest trauma it is surprising that haematemesis does not occur more frequently The possibility must always be borne in mind that the haemorrhage when seen may come from co-existing peptic ulcers in the stomach or duodenum It has been suggested by some authors that congestion of the gastric mucosa in the herniated stomach may cause haemorrhage but as no evidence of any gross congestion is seen either at oesophagoscopy when the mucosa can be directly viewed through the patulous cardia or when the vessels supplying the thoracic portion of stomach are inspected at operation it may be yet another of those attractive theories which can be so wrong in medicine



FIG 38—Barium swallow of child of 3½ years with chronic anaemia and severe substernal pain Oesophagoscopy confirmed the presence of a hernia complicated by reflux oesophagitis and chronic superficial ulceration The haemoglobin returned to normal following repair of the hernia

Anaemia—Hiatus hernia has at last been recognized as an important cause of anaemia especially in infancy and childhood Numerous reports of isolated cases of severe anaemia associated with hiatus hernia and no other discernible source of haemorrhage have appeared Ritchie and Winsauer (1947) have reviewed the incidence in a number of reported series of cases of diaphragmatic hernia and find an incidence of anaemia varying between 3 4 and 66 per cent average 20 per cent and of haemorrhage between 2 5 and 33 per cent average 17 per cent in different series The type of hernia is not always specified but it may safely be assumed that the majority were of the hiatus variety The criteria of anaemia adopted by Ritchie and Winsauer were a haemoglobin of less than 12 grams per cent in men and less than 11 grams per cent in women Murphy (1942) reported 7 cases of macrocytic anaemia and 40 cases of secondary anaemia in a serie of 67 cases of hiatus hernia Ernstene and McGurl (1940) found only 2 cases of hypochromic anaemia in 59 cases of hiatus hernia In 60 of Harrington s cases the incidence was 11 per cent and in 221 cases reported from the Massachusetts General Hospital the incidence

was 12 per cent The anaemia is usually of the hypochromic microcytic type and responds well to iron Adopting Ritchie s criteria of anaemia the incidence in the Frenchay series was 22 per cent but 7 of the 14 children suffered from this complication In only half the anaemic patients was there any evidence of oesophageal ulceration and although this would appear to be the most likely cause of the anaemia this explanation is too simple although it may be valid for children A deficient diet may contribute to the anaemia but no appreciable weight loss accompanies it Mitchell (1950) suggests toxaemia secondary to intestinal obstruction as a cause and quotes the work of Cameron Watson and Witts (1950) who were able to produce anaemia in rats by forming blind intestinal loops the essential feature being stagnation of intestinal contents but the anaemia produced was of the macrocytic type

Carcinoma —Malignant disease of the lower oesophagus or cardia may be found in association with a hiatus hernia Both diseases are common and the association when it occurs may be fortuitous Smithers (1950) has reviewed the association but the number of cases he has collected is small and no greater than would be expected on the assumption that the relationship is accidental There is no evidence that chronic reflux oesophagitis is a pre malignant condition and chronic peptic ulceration of the intrathoracic portion of the stomach shows no greater tendency to malignant degeneration than usual Smithers advances the theory that the growth may be one of those upper abdominal lesions that are supposed to cause reflux contraction and shortening of the oesophagus and that the growth may be responsible for the hernia



FIG 39 —Hiatus hernia associated with a carcinoma of the cardia involving the lower third of the oesophagus

Concomitant disease—One reason why the pathological significance of hiatus hernia and the misery it can cause the patient have occasioned so little clinical interest in the past has been the frequent co existence of other lesions abdominal cardiac or mediastinal and these have tended to mask the hernia as the culprit The patient s distress was attributed to the small cluster of gallstones the hypotonic stomach or to some occult cardiac condition vaguely suspected When improvements in radiological technique began to bring these hernias to light there was still no move to assign to them any responsibility for the patient s symptoms As recently as 1947 Radloff and King in reporting on 50 cases of hiatus hernia stated

In 68 per cent concomitant disease was found and was often responsible for the symptoms Only 30 per cent had symptoms that could be attributed to the hernia Surgery was necessary in only 3 cases They concluded Diaphragmatic hernia is usually an insignificant finding and is unusually asymptomatic

This is a very different story from that told by patients admitted to Frenchay Hospital with this condition 67 out of 80 adult patients accepted with alacrity the offer of surgical treatment all other methods of treatment including various abdominal operations having failed to produce relief and of the remaining 13 cases few were rejected because it was considered that the symptoms were too mild to justify surgery Of 14 children surgical treatment was imperative in 13 on account of the complications of the hernia—oesophageal strictures haemorrhage anaemia and duodenal obstruction

One of the most difficult problems for the clinician confronted by a patient with a radiologically demonstrated hiatus hernia is the assignment of the patient s various symptoms to the underlying lesions present and only careful consideration of the differential diagnoses and a complete and thorough investigation to exclude these can save the clinician from a sometimes tragic error and the patient from an unnecessary operation In not a few cases the problem will be simplified for *him* as a result of most of the other organs usually incriminated by the clinical picture having previously been removed this latter method of diagnosis by exclusion is not to the patient s advantage

Hiatus hernias first came under suspicion as a prolific cause of subjective distress when the pioneer work of Allison first implicated the hernia in the aetiology of such obvious disabilities as gross stenosis of the oesophagus repeated gastro-intestinal haemorrhage anaemia and duodenal obstruction complications which can hardly be assigned to gallstones chronic appendicitis diverticulosis of the colon for instance

Equally grave is the danger of neglecting to prove by complete investigation the absence of pathology elsewhere in the heart or gall bladder for example which could be responsible and the possibility of a composite picture due to the presence of several lesions must be borne in mind Brick found associated lesions capable of causing symptoms in one in every four patients in his series of 308 cases Harrington reports that in every one of his cases an average of 3 previous diagnoses had been made and in 10 per cent previous operations had been undertaken but with what justification he does not state Clerf Shallow Putney and Fry (1950) state that errors in previous diagnosis had been made in 35 of their 110 cases and list these diagnoses they state that an unspecified number of their cases not included amongst the 35 had multiple lesions— cholecystitis with or without gallstones coronary artery disease duodenal ulcer or traction diverticulum

Gilbert Dey and Rall (1946) in search of associated lesions in support of the theory that a vagal reflex and oesophageal spasm are the cause of the hernia, found 27 upper abdominal and thoracic lesions amongst their 48 cases and these are listed in Table III

TABLE III

Upper Abdominal and Thoracic Lesions—Gilbert Dey and Rall

Cholelithiasis	10
Cholelithiasis and obesity	3
Cholelithiasis duodenal ulcer and obesity	1
Duodenal ulcer	5
Oesophageal diverticula	4
Oesophageal diverticula and obesity	1
Duodenal diverticula	1
Carcinoma of stomach	1
Tumour involving diaphragm	1
	27

The hazards of diagnosis are well illustrated by the following case A man of 59 years suffering from the characteristic symptoms of hiatus hernia but rather more dyspnoea than is usual with this condition was referred to a thoracic unit for oesophagoscopy and further investigation He had previously been seen by a cardiologist on account of his dyspnoea and the heart pronounced as normal On the day before his admission he dropped dead in a cinema Autopsy revealed a hiatus hernia and gross aortic valvular stenosis

Symptoms

The following description by Allison of the clinical picture in a typical case of *hiatus hernia* complicated by reflux oesophagitis cannot be bettered so it is reported here at length

> A woman of 59 years of age complains that for 6 years she has suffered from intense burning pain behind the lower part of the sternum which rises up towards or even into the neck It may spread into the jaw the ear or the hard palate or radiate through to the back between the shoulder blades or down the arm It comes on especially when she exerts herself stooping forward as in washing the floor bending over the wash tub poking the fire or fastening her shoes It wakes her in the middle of the night especially if she is sleeping on her back or her right side and she seeks relief from what she describes as an agonizing pain by sitting upright and taking a few sips of water milk or alkaline mixture She says that her throat usually feels dry and burning When she swallows she may be conscious of the passage of food down the gullet it may cause a feeling of soreness and may sometimes lodge towards the lower end of the sternum causing pain which is immediately relieved as the bolus passes into the stomach If she bends forward after a meal food or sour fluid rises into her throat and has to be swallowed again Her husband says that for belching she takes the first prize Four years ago she was thought to have cholecystitis but removal of either a normal or abnormal gall bladder did not cure her Radiography of her stomach and duodenum shows no evidence of ulcer She has tried all the advertised stomach medicines with only temporary relief and has finally been told that the nerves of her stomach have been upset by the change of life

This story with minor variations occurs often enough in the hospital out-patient department to deserve more notice and better treatment

Pain epigastric and substernal is the commonest symptom from which the patient seeks relief even in the uncomplicated case where no oesophagitis is present When oesophagitis and peri oesophagitis occur the pain extends through to the back in the mid line Stooping almost invariably aggravates the pain and the patients usually discover for themselves that they must sleep propped up to obtain any relief

Chronic heartburn is another frequent and distressing symptom that appears to be pathonomonic of hiatus hernia

Regurgitation of recently ingested food may occur intermittently and without warning usually at the commencement of a meal Regurgitation brings relief and the patient may then be able to return to the table and finish the meal without discomfort Some patients say that they are afraid to eat others that they avoid social engagements on account of the embarrassment caused by the regurgitation The appetite remains good and weight loss is uncommon Most female sufferers are obese and some are gaining weight in spite of their disability



FIG 40 —Barium swallow of infant of 5 months suffering from repeated vomiting haematemesis and anaemia The infant had gained only 2 pounds in weight since birth

The dysphagia that occurs is of two types depending upon the stage of the oesophageal inflammation In the stage of acute ulceration the complaint is of the food sticking in the lower retrosternal regional When secondary stenosis has developed swallowing is followed immediately by more severe distress and prompt regurgitation much mucus is regurgitated especially first thing in the *morning The obstruction may suddenly become complete and the patient is then* admitted to hospital as an emergency usually with a diagnosis of carcinoma of the oesophagus

Many patients complain of shortness of breath but whether more so than patients of similar build without hernias is difficult to determine

There is one type of pain associated with a hernia and undoubtedly caused by it which may resemble the pain of angina The patient complains of acute praecordial pain or distress coming on in spasms and radiating up to the left or both sides of

the neck and down the left arm but the pain usually follows eating and is not related to exercise Nuzum (1947) reported an incidence of 25 patients with hiatus hernia in 100 private patients diagnosed as having angina pectoris Gilbert (1948) found an incidence of 18 or 17 per cent with angina like pain in 107 patients with hiatus hernia

The clinical picture of hiatus hernia in infancy and childhood is not yet generally recognized but is sufficiently typical to deserve more attention The incidence of ulceration and stenosis is higher than in adults but in other children with un complicated hernias the diagnosis may frequently be missed Regurgitation and vomiting commence soon after birth and the infant fails to thrive A diagnosis of pyloric stenosis is often made Some degree of anaemia is almost always present and may be severe occasionally the anaemia is the presenting sign of the hernia At the age of three months the feeding may get easier and the infant gain weight but between the sixth and twelfth month regurgitation returns and becomes pro gressively worse The infant loses weight again and is admitted to hospital for an emergency gastrostomy with complete obstruction of the lower oesophagus

In the infant or child with Type IIA hernia with the whole stomach above the diaphragm the symptoms are less severe and intermittent with bouts of vomiting due to duodenal obstruction Anaemia is uncommon in this type and oesophageal ulceration and stenosis are rare In this type the angle of entry of the oesophagus into the stomach is acute and the bulk of the intrathoracic stomach may cause sufficient pressure on the lower end of the oesophagus to prevent reflux of gastric contents recurring

The symptoms of the congenital short oesophagus are those of Type I hiatus hernia with a patulous cardia and no clinical means of differentiating between these two conditions exist

Diagnosis

Clinical diagnosis

The history and the symptoms present a clinical picture which is now regarded as characteristic of hiatus hernia and which enables a provisional diagnosis to be made with fair accuracy Any patient complaining of chronic heartburn inter mittent regurgitation dysphagia and substernal or epigastric pain aggravated by stooping or lying flat should be subjected to the routine investigations necessary to confirm the diagnosis

There are no characteristic physical signs of this condition *The female sufferers* are usually obese and appear in good health despite the bitterness of their com plaints Anaemia may be apparent but examination of the chest and abdomen is usually negative

Radiological diagnosis

The radiological technique for the demonstration of the intrathoracic part of the stomach and the cardia has been well described by numerous authors since Soresi s first account in 1919 The procedure might well be described as reflux oesophago graphy The patient first swallows a glass of barium suspension Screening in the erect position will probably fail to reveal any abnormality at the cardia unless

secondary stenosis is already present The patient is then tilted into the prone head low position and the barium bolus will then be seen to distend the intrathoracic portion of stomach and flow through the patulous cardia into the oesophagus Shanks states that asking the supine patient to raise his legs or head off the table while continuing to breathe will raise the intra abdominal pressure and cause a reflux of the barium upwards Screening with the patient bending forward in the stooping position may also reveal the hernia

Barium examination will show how much of the stomach has herniated the position of the cardia and the angle of entry of the oesophagus into the stomach It will reveal the position and degree of any secondary stenosis and the reflux procedure will outline the lower end of the stricture and show its length It may also show the presence of chronic peptic ulceration in the intrathoracic part of the



(a)



(b)

FIG 41 —(a) Skiagram in the supine position of an infant of 1 year with a Type IIa hiatus hernia the shadow suggests a solid tumour (b) barium meal in the same case showing duodenal obstruction (*By courtesy of the British Medical Association*)

stomach What it will not reveal however are the reflux oesophagitis and superficial ulceration and the real length of the oesophagus The oesophagus that looks short on barium examination in the absence of any stenosis which usually accompanies secondary acquired shortening due to fibrosis very rarely is short Chronic peptic ulcer of the oesophagus is a diagnosis not infrequently made by the radiologist but rarely confirmed by the endoscopist Any inference regarding spontaneous reducibility of the hernia drawn from screening in varying positions is also liable to be quite fallacious in the light of operative findings

The Type I hernia can rarely be seen in the straight antero posterior and lateral skiagrams but Types II and IIA will appear as cystic air containing shadows in the posterior mediastinum behind the heart shadow especially in the lateral film When the whole stomach lies above the diaphragm the bulk of it projects into the right pleural cavity and may cause some diagnostic confusion It should be re membered that these shadows only contain fluid levels when the patient is radio logically examined in the erect position

Endoscopy

No investigation has revealed more of the essential pathology of hiatus hernia and the mechanics of its complications than oesophagoscopy the fact that so little attention has been paid to this procedure and its revelations in the past is due to our ignorance of so many aspects of this disease till the present time There is little or no mention of this manoeuvre in the majority of papers on this subject nor of the complications it reveals As stated previously little progress was made till thoracic surgeons and others interested in this subject undertook to perform their own oesophagoscopic examinations Many cases of reflux oesophagitis and secondary stenosis must have been examined by ear nose and throat surgeons in the past but with the exception of Moersch and Clerf few have called attention to these lesions One can only assume that in those cases where a stricture was seen an erroneous diagnosis of malignant disease was made in the majority and these cases may explain some of the claims of cure of carcinoma of the oesophagus by deep x ray therapy after a preliminary gastrostomy

The endoscopic appearances vary with the stage of the disease In the un complicated hernia the most striking finding is the patulous cardia The instrument can be passed through the cardia into the stomach without any difficulty provided the instrument is long enough and 56 centimetres is suggested as a minimum length for this purpose The cardia which may already be wide open tends to dilate further during inspiration and the greatest tendency to reflux occurs during this phase when the negative intrathoracic pressure falls Much of the intra thoracic stomach can be explored through the oesophagoscope

By contrast the normal cardia usually presents an efficient barrier to the passage of the instrument and entirely different appearances during the phases of normal respiration On inspiration the crura contract and close the diaphragmatic pinch cock thus resisting the raised intra abdominal pressure During expiration the pinch cock relaxes and swallowed air can be heard escaping through it from the stomach into the oesophagus small volumes of gastric secretion may also rise into the lower oesophagus during expiration

One of the advantages of performing oesophagoscopy under local anaesthesia is that the patient retains voluntary control of his breathing and can demonstrate the full range of activity of the crura during the examination

The appearances of the cardia are characteristic and with increasing experience oesophagoscopy may come to precede radiology as the first means of diagnosing not only the presence of hiatus hernia but of other abnormalities of this region such as the lax hiatus and patulous cardia which may be accompanied by no herniation of the stomach visible on radiology but which may be associated with the reflux oesophagitis and other complications frequently caused by a hernia

Every patient with symptoms suggestive of a hernia or with some undiscovered source of haemorrhage should be oesophagoscoped

The endoscopic appearances of reflux oesophagitis are striking and typical The mucosa of the lower end of the oesophagus is hyperaemic and oedematous along the crests of the vertical rugae are superficial ul ers with a fiery red margin and a central pale grey sloughing membrane which is nonadherent and can be gently wiped off with a swab leaving a raw profusely bleeding surface The ulcers may extend to the troughs between the rugae and coalesce they may extend upwards to the junction between the middle and lower thirds but at this point there is usually a sharp line of demarcation between the normal and the ulcerated mucosa During the examination the mucosa is repeatedly obscured by gastric contents welling up through the cardia especially with the patient in the horizontal position and for this reason the examination can be more satisfactorily performed with the patient sitting up in a dental chair

In the chronic phase stenosis follows the ulceration There is concentric narrowing of the oesophagus but little loss of normal mobility The margins of the stricture are ulcerated and narrow finger like ulcers may extend above its level for a short distance Again there is a sudden change from the normal appearances of the middle third to those of the diseased segment Dilatation of the stricture causes prompt haemorrhage and reveals that the mucosa has been completely destroyed in the stenosed segment a fact which can be con firmed by examining biopsy specimens from various points along the length of the stricture

Occasionally healed fibrous strictures are seen with no visible active ulceration These may be concentric and almost complete or crescent shaped and partial denoting that ulceration has been present in the past This information is of importance in that the scarring of the mucosa will almost certainly be accompanied by considerable old peri oesophagitis and adhesions to the mediastinal tissues as well as some degree of acquired secondary shortening These appearances suggest that spontaneous healing of the superficial ulceration can occur

Laboratory investigation

A full blood-count and haemoglobin estimation are necessary in every case The plasma proteins should be estimated in every case to be submitted to surgical treatment The benzidine reaction of the faeces for occult blood should be deter mined in the absence of any endoscopic evidence of oesophageal ulceration a positive reaction may indicate concomitant ulceration elsewhere in the gastro intestinal tract

A fractional test meal repeated on several occasions and accompanied by radiological evidence of the presence of the tube within the stomach will con tribute not only to our knowledge of the effect of hiatus herniation upon gastric function but also to the selection of the correct surgical treatment

Diagnosis by exclusion

Lack of positive evidence of other lesions such as duodenal ulceration chronic cholecystitis coronary disease may contribute to the diagnosis

Therapeutic tests

There is no satisfactory test as non operative therapeutic measures which will relieve the symptoms of hiatus hernia will improve the symptoms of other conditions which may confuse the diagnosis

However the relief obtained by the patient sleeping propped up on 5–6 pillows is suggestive of hiatus hernia

Exploratory operation

The results are less satisfactory than would be expected Exploratory laparotomy has in the past often been declared negative in the presence of a hernia The sac is small and only the cardia may have herniated Digital examination of the hiatus from below may leave the operator with no clear impression of any abnormality Surprisingly exploratory thoracotomy has also failed to reveal a small sliding hernia to the uninitiated on account of the striking similarity in the external appearances of the herniated portion of the stomach and the normal oesophagus In the presence of secondary fibrous stenosis only a little thickening may be palpable in the wall of the oesophagus in the region of the stricture and the degree of stenosis cannot be estimated from the external appearance of the organ

Differential diagnosis

Gastric and duodenal ulceration —The clinical picture is sufficiently distinct from that of gastric or duodenal ulceration to enable these conditions to be differentiated on the history alone in many instances Difficulty occurs when as not infrequently happens the two conditions co exist but the increasing use of oesophagoscopy and the routine employment of the prone head low manoeuvre during the radio logical examination of the upper gastro intestinal tract should lead to greater accuracy in diagnosis

Carcinoma of the oesophagus and cardia

Patients with secondary fibrous stenosis of the lower third of the oesophagus which may cause obstruction of rapid onset in the fifth to seventh decades are frequently referred to hospital with a provisional diagnosis of carcinoma of the oesophagus It is probable that in the past when the conception of oesophagitis and non malignant stenosis was unknown to many endoscopists no differentiation was attempted and all these strictures were classified as malignant The dawning appreciation of the frequency of hiatus hernia and its complications should lead to the more intelligent use of the oesophagoscope and fewer errors in diagnosis

Carcinoma may complicate a hernia but in these circumstances the latter condition is of no clinical importance Carcinoma of the body of the stomach may be suspected in a case of hernia complicated by anaemia

Achalasia of the cardia

Dilatation of the oesophagus is rare in hiatus hernia even with stenosis and usual in achalasia The symptoms are different and the response to octyl nitrite is diagnostic of achalasia

Congenital atresia of the oesophagus

Strictures of the lower oesophagus in infants and children were usually regarded as congenital abnormalities till Allison drew attention to the underlying hernia and ulceration.

The incons stency of complete developmental stenosis or atresia occurring in the upper third of the oesophagus and a partial degree of what was regarded by many as the same cond tion in the lower third, unfortunately did not arouse the curios y of the paediatricians sufficiently to stimulate a search for other explanations.

Congenital short oesophagus

This condition may be suspected on oesophagoscopy but can only be differentiated from the Type I hiatus hernia by thoracotomy and surgical exploration of the oesophagus.

Pyloric stenosis

The repeated regurgitation and vomiting in the infant with hiatus hernia may lead to a diagnosis of congenital pyloric stenosis. No abdominal tumour is present and the vomiting is more intermittent in the infant with a hernia; moreover the vomit is frequently blood-stained. The radiological diagnosis of oesophageal abnormalities in infants is notoriously difficult, and here again oesophagoscopy may be of great value. Brown Kelly has described a condition of idiopathic dilatation of the lower oesophagus in infants due to failure of the muscle to develop but most of his observations were based upon autopsy material.

Other types of diaphragmatic hernia

Herniation through the patent pleuro-peritoneal canal, through the foramen of Morgagni, through the defect of congenital absence and the traumatic hernia, do not give rise to reflux oesophagitis, and its complications. The symptoms of these conditions are caused by intermittent intestinal obstruction due to volvulus or kinking, normally at the level of the duodenum or lower; pulmonary and circulatory embarrassment may be caused by the volume of the intestine within the thorax but this rarely occurs with a hiatus hernia. These abnormalities should be differentiated easily on radiological examination.

It is rare for any organ other than the stomach to herniate through the oesophageal hiatus; in the other types of diaphragmatic hernia the stomach is usually the only organ to remain wholly within the abdominal cavity, most of the other viscera lying partly or entirely within the pleural cavity.

Cholecystitis

Of all the concomitant diseases that occur cholecystitis is probably the commonest, and the flatulent dyspepsia associated with it bears some resemblance to the disturbance caused by a hiatus hernia. Dunhill reports the finding of gall stones in 16 per cent of his cases of hiatus hernia. In the latter condition, jaundice does not occur; the pain is characteristically situated in the epigastrium in the mid-line or in the lower substernal region, not in the right upper quadrant, and is described as burning rather than colicky in nature. Heartburn is more suggestive of a hernia than of cholecystitis. Differentiation of these two conditions on clinical

grounds alone however is fraught with difficulty and every suspected sufferer should be fully investigated by all available means for both conditions When both are present, and in the absence of complications rendering surgery imperative the decision as to which of the two conditions has the prior call on treatment must be left to the acumen and common sense of the clinician

Chronic appendicitis

Chronic appendicular dyspepsia has always been an unsatisfactory diagnosis carrying little conviction and scant pathological justification when the organ has duly been removed and examined by the histologist the diagnosis has frequently been resorted to in the past for want of an alternative The diagnostic methods available for revealing the presence of a hiatus hernia may now lead to the disappearance of this unsatisfactory diagnosis there is little evidence to justify its retention as a clinical entity

The functional abdomen

This again is a diagnosis to which the harassed clinician need turn with diminishing frequency Many cases so labelled in the past as the result of an uninformative exploratory laparotomy were undoubtedly suffering from a hiatus hernia The mere appreciation of the commonness of the latter condition should save the clinician from many of these unhappy pit falls in the future Now that the profession is emerging from the period of diagnostic adolescence the diagnosis of functional abdomen like that of chronic appendicular dyspepsia should be invoked with diminishing frequency

Angina

As has been stated earlier patients with hiatus hernias may suffer pain which on cursory questioning bears some resemblance to the pain of true angina of effort in so far as it is praecordial in origin and radiates up to the neck usually on the left side and down the left arm The pain is referred to those areas supplied by the same spinal segments as the phrenic nerve and may be caused by mechanical stretching of the hiatus by gaseous distension of the stomach or mechanical stimulation of the phrenic in some other way The angina like pain of hiatus hernia is related more to meals and not to effort and this is the most significant point differentiating it from true cardiac angina The electrocardiographic changes typical of coronary disease are absent in the case of hiatus hernia

Globus hystericus

Several patients in the Frenchay series were referred to hospital with this diagnosis When some degree of obstruction is present the patient may refer the symptoms to the region of the throat The diagnosis of globus hystericus *should* rarely if ever be made certainly not before complete radiological and oesophagoscopic examination

Cystic lesions of the mediastinum

The Type II or IIA hernia *Allison s rolling type may be visible in antero* posterior and lateral skiagrams as a cystic air-containing shadow in the posterior

mediastinum behind the heart shadow or when most of the stomach lies above the diaphragm projecting into the right pleural cavity from the mediastinum This type which may be picked up on mass radiography may be confused with other cystic shadows at the base of the lungs such as chronic lung abscess lung cyst oesophageal diverticulum emphysematous bulla If the skiagram is taken with the patient lying horizontally and the herniated stomach contains fluid the shadow may appear solid and resemble a tumour

A barium-swallow should easily differentiate these conditions from a hiatus hernia

Anaemia

In some cases of hiatus hernia the presenting sign is anaemia and in this group other causes of anaemia must be excluded The anaemia found with a hiatus hernia is of the secondary hypochromic type but it is not consistently associated with oesophageal ulceration and haemorrhage Anaemia is a more common complication of hiatus hernia in infancy and childhood than in adult life and any child suffering from anaemia should be investigated for a hernia

Prognosis

There is no evidence that an uncomplicated hiatus hernia in an adult shortens the normal span of life but the morbidity rate in terms of discomfort and distressing complications is high In infants and children the higher incidence of major complications such as oesophageal obstruction increases the risk to life and renders obligatory forms of surgical treatment that are not devoid of peril to the patient Harrington reported 7 operative deaths in 343 cases treated surgically an incidence of 2 per cent Allison 1 death in 48 cases In the Frenchay series of 77 operations including 51 repairs and 21 oesophago-gastric resections and anastomoses for secondary strictures there were 6 operative deaths Three of the deaths were due to pulmonary embolism and one to subarachnoid haemorrhage of unexplained aetiology one patient died of cardiac failure with auricular fibrillation and another from broncho-pneumonia due to staphylococcal infection resistant to both penicillin and streptomycin Of 13 cases all adults treated medically without operation 2 died one from perforation of an acute high lesser-curve gastric ulcer into the hernial sac and the other from massive haemorrhage from two acute lesser-curve gastric ulcers

The prognosis following surgical treatment must still be approached with some reserve as the number of cases that have been followed up for an adequate period following operation is still relatively few The initial results of repair are good and the relief of symptoms is often dramatic Among the 51 cases repaired at Frenchay Hospital there have been 7 unsatisfactory results traceable in every instance to some technical fault—incomplete reduction at time of repair paralysis of the diaphragm anterior displacement of the oesophagus into the tendinous pouch of the diaphragm or unwarranted interference with the vagus nerves Of the 21 cases submitted to resection all have been relieved of their obstruction dysphagia and other symptoms of chronic oesophagitis in one case a mild degree of acute oesophagitis occurred after operation despite resection of the upper half of the stomach but was controlled by medical measures



(a)

FIG 42—Type II hernia converted to Type I by incomplete reduction Reflux oesophagitis developed after the operation *and persisted till complete* reduction and repair had been achieved at a second operation (*a*) Before operation (*b*) after incomplete reduction



(b)

Treatment

The symptoms of hiatus hernia and those of its complications are caused by the mechanical failure of a normal physiological sphincter between the oesophagus and stomach The functioning of this sphincter depends upon the muscular activity of those portions of the diaphragmatic crura forming the margins of the hiatus and upon the correct anatomical relationship of the cardia to the hiatus Treatment must aim at the restoration of the diaphragmatic pinch cock and the cardiac sphincter surgical reduction of the hernia and repair of the hiatus in such a way that its normal action on the oesophagus is restored is surely the only rational approach

It is difficult to understand how medical treatment can offer more than palliative or psychological relief for an abnormality so essentially mechanical in origin Two measures may lessen the tendency to reflux oesophagitis—the buffering of the abnormally high gastric acidity and peptic secretion by alkalis and frequent small meals and by encouraging the patient to sleep propped up on 5-6 pillows

Bearing in mind the essential requirements for correction of the physiological and anatomical defect certain operative procedures still frequently employed appear to be basically unsound (a) paralysis of the diaphragm (b) anterior displacement of the cardia to the tendinous portion of the diaphragm (c) anterior or lateral repair and (d) any gross interference with or strangulation by tight suturing the muscle fibres of the crura

The aim of the operation is to eliminate the patulous cardia by restoring the diaphragmatic pinch cock and this aim is defeated if the essential muscular mechanism is paralysed or otherwise ruined Dunhill however recommends phrenic crush as a preliminary to repair and Pickhardt Rafsky and Ghiselin (1950) regard it as an effective method of treatment Guthrie and Jones advise it as a palliative and pre operative measure but admit that the patient s symptoms are not relieved The evaluation of any method of treatment depends upon the care and length of the follow up survey a point still sadly neglected in many clinics and those authors who advocate a phrenic crush as a definitive method of treatment do not state whether the symptomatic relief persists as long as the diaphragmatic paralysis

In advocating surgical repair of the hernia as the rational treatment for this condition the importance of complete reduction cannot be overstressed In complete reduction may convert a Type II hernia into the far more dangerous Type I and lead to reflux oesophagitis and its complications For this reason recurrent hernias—usually incompletely reduced hernias—cause distressing symptoms that seriously reflect upon the wisdom of advocating surgical repair An incomplete operation is worse than no operation at all

Once secondary shortening and stenosis have occurred two distinct problems arise first relief of obstruction and restoration of normal swallowing secondly the prevention of further reflux and oesophageal ulceration at a higher level Even when secondary shortening is not so gross as to render repair of the hernia im possible this procedure cannot restore a normal oesophageal lumen most strictures do not respond well to repeated dilatation as the chronic ulceration becomes aggravated by the trauma and further fibrosis results When the stenosis is suffi ciently severe to cause dysphagia resection of the diseased segment is indicated



FIG 43.—Skiagrams showing tendency of hernia to increase in size following phrenic crush (*a*) Before operation (*b*) after operation

(*a*)



(*b*)

As to how best to restore bowel continuity and eliminate the risk of further reflux and ulceration—this operation does not restore a sphincter between oesophagus and stomach—opinions differ widely at the present time

Gentle dilatation may be attempted in patients in whom major surgery is contra indicated but it may have to be repeated at diminishing intervals and with in creasing difficulty at each attempt

Indications for surgical treatment

As early as 1853 Henry I Bowditch a visiting physician at the Massachusetts General Hospital in a review of the literature and the presentation of a case of diaphragmatic hernia suggested that surgery might be tried as a last resort in the treatment of this disease because of the poor results obtained by the use of emetics leeches cathartics venesection bathing and ether (Soutter 1947) This view is still held by some physicians

That there is still no general agreement on the indications for operation is shown by the widely divergent views expressed by various authors and by marked difference in the percentage of cases submitted to surgical treatment in reported series Radloff and King (1947) decided that only 3 of their 50 cases needed surgical treatment Stapleton (1947) is of the opinion that only the large hernias require surgical treatment but this view is at variance with the observations of Allison and others that it is the small hernias of the sliding type that are most frequently complicated by oesophagitis and its sequelae and give rise to the most trouble if not repaired Examination of Allison s papers suggests that he is widening his indications and tending to advise surgical treatment in an increasing number of his cases Of 73 patients with the sliding type of hernia complicated by oesophagitis 33 were treated by surgical repair in 15 of 63 patients with secondary stenosis resection and oesophago jejunostomy were performed Of the 94 cases admitted to Frenchay Hospital surgical treatment was advised and willingly accepted by the patient in 80 repair was performed in 54 cases and oesophago gastric resection with restoration of bowel continuity in 23 and 2 children have had gastrostomies performed preparatory to a resection In this series the presence of reflux oeso phagitis and its complications have been regarded as definite indications for surgical treatment in view of the tendency of oesophagitis to become chronic and proceed to stenosis if allowed to continue untreated In the uncomplicated cases operation has been advised in Type I hernias on account of the greater risk of oesophagitis in this group Of the others those patients who considered that their symptoms were sufficiently distressing to warrant operation were treated surgically Once the patient is aware of the risks and inconvenience involved by surgical treatment and the probable results of treatment he or she is in a position to assist the clinician in reaching a decision in this difficult borderline group of cases

Another indication for operation is the patient s anxiety to be relieved of any further waste of time and money being unsuccessfully treated for other conditions diagnosed in error

Operation was necessary in 13 of the 14 children in the Frenchay series the indications being duodenal obstruction in 2 haemorrhage and anaemia in 2 and severe oesophageal obstruction in 9 Repair was performed in 4 children and resection in 7 2 other children have had preliminary gastrostomies and are

awaiting resection All but two of the children with secondary stenosis were admitted to the hospital at the age of 9 months to 1 year with complete oesophageal obstruction *and surgical treatment had to be carried out as an emergency in one* repeated dilatation was possible as a preliminary to resection but in the remainder a temporary gastrostomy performed as near the fundus as possible in order to reduce or eliminate skin excoriation was preferred to a jejunostomy owing to the greater ease of feeding One child with gross stenosis and dysphagia was admitted to hospital at the age of 5 years having been treated for hysteria for the previous 4 years The presence of a gastrostomy does not seriously complicate the subsequent resection the gastric fistula being closed during the mobilization of the stomach Early repair of the hernia during infancy will lead to heal ng of the oesophageal mucosa and the prevention of subsequent stenosis as in adults

It is more difficult to decide if and when to operate on the infant or child with an uncomplicated hernia and minimal symptoms An increase in size of the hernia as revealed by routine barium swallow examinations is not alone an indication for surgery as the larger hernias are relatively less harmful than the smaller Any increase in the vomiting and regurgitation sufficient to interfere with the nutrition of the child or the onset of oesophagitis should prompt the consideration of operation before the general condition of the child deteriorates to the stage when operation becomes dangerous

Once secondary stenosis has occurred the problem is one of treating not a simple fibrous stricture of the oesophagus but of chronic ulceration as well as a structure Dilatation therefore is not indicated as an elective form of treatment In only 1 of the 14 children treated by the author was the ulceration sufficiently healed to warrant dilatation of the resulting stricture When chronic ulceration is present the passage of a bougie becomes progressively more difficult despite the utmost gentleness in its manipulation and resection eventually becomes necessary In one case dilatation had been adopted as the method of choice for the relief of dysphagia The stricture had been dilated under general anaesthesia every month or two till the child a girl was 8 years old she was then taught to pass a bougie upon herself every morning before breakfast By the age of 15 years the child was under nourished a psychological wreck and swallowing with difficulty through a rigid tube of fibrous tissue completely devoid of any mucosa Resection of the stenosed oesophagus together with the upper half of the stomach followed by an oesophago gastric anastomosis at the level of the aortic arch have completely relieved the dysphagia and malnutrition and have been instrumental in the return of the girl s mental state to normal

Having performed an emergency gastrostomy how long one should wait before performing the resection depends more upon the mental development of the child than any other factor Assuming that a gastrostomy is highly undesirable on every count it should be dispensed with at the earliest opportunity but it is inadvisable to undertake any major thoracic operation till such time as the child is able to co operate with the nursing staff physiotherapists and surgical residents during the post operative period Prognosis will depend upon the child s ability to cough when instructed to do so and to tolerate an intravenous drip or an intercostal catheter without struggling to free himself from these incumbrances The age at

which the child achieves this ability to co operate varies widely the average age is four years

In the adult patient with complete or near complete obstruction a preliminary gastrostomy or jejunostomy is best avoided Although suffering from chronic starvation the patient s general condition remains surprisingly good A 2 pint slow drip blood transfusion is given irrespective of the haemoglobin level as the plasma proteins are usually low after 3–4 days of intensive breathing exercises oral toilet such as scaling and removal of infected tartar and debris from the gums and teeth restoration of fluid and electrolyte balance a primary resection of the stenosed oesophageal segment is performed followed by an oesophago-gastric or oesophago-jejunal anastomosis

There is one group of cases where selection of the operative procedure presents difficulties Cases are seen where there is a mild degree of secondary stenosis insufficient to cause dysphagia but associated with a degree of secondary fibrosis and acquired shortening of the oesophagus that renders complete reduction and repair of the hernia difficult or impossible It has been suggested that paralysis of the diaphragm may allow it to be drawn up to a cardia which cannot be drawn down This suggestion however cuts right across the assumption that successful repair depends upon the restoration of normal physiology as w ll as normal anatomy Compensation for the shortening by creating an artificial hiatus at a higher level in the tendinous part of the diaphraem equally fails to restore the muscular diaphragmatic pinch cock Paralysis of the diaphragm should be avoided and if extensive freeing of the oesophagus from the mediastinum does not permit the cardia to be replaced below the diaphragm without tension then a resection and high anastomosis accompanied by some manoeuvre to reduce the risk of recurrent oesophagitis such as resection of the upper half of the stomach or exclusion of the stomach is probably indicated It must be remembered that this group of patients is suffering from the distress of chronic oesophagitis and that the stenosis may get progressively worse Nice judgment and common sense are called for on the part of the surgeon confronted by this state of affairs at operation

Technique of repair

Approach

The early developmental work on the repair of hiatus hernias was done by the general surgeons and the abdominal approach was therefore the method of choice A high left paramedian incision combined with forcible retraction of the costal margin gave a fair exposure of the hiatus but little or no access to the posterior mediastinum Moreover the underlying congenital abnormality of the crura of the diaphragm was not apparent through this approach and the posterior repair now accepted as the rational m thod of restoring the mechanical efficiency of the diaphragmatic pinch cock was not developed till the hiatus was approached and viewed from above The usual repair by the abdominal route was a lateral cobbling of the margin of the hiatus by sutures of silk and or fascia Great attention was paid to the excision of the sac

Unfortunately the frequent occurrence of oesophagitis peri oesophagitis and adhesions to the surrounding mediastinal structures rendered reduction by traction from below dangerous difficult and sometimes impossible It rendered any

observation of the condition of the oesophagus well nigh impossible and contributed little to our knowledge of the basic pathology of the condition

The advantages of the thoracic approach which is now gaining in popularity are (i) adequate exposure of the herniated stomach and oesophagus which can be freed from the mediastinum under direct vision if necessary (ii) evaluation of any true or apparent shortening of the oesophagus (iii) ease of access for repair of the posterior margin of the hiatus by approximation of the crural fibres behind the oesophagus (iv) can be extended easily into a combined abdomino thoracic approach if necessary (v) lower incidence of post operative chest complications by interfering less with the cough mechanism and (vi) possibly a lower recurrence rate

Soutter (1947) has followed up the results of 62 operations performed for the relief of hiatus hernia by various surgeons at the Massachusetts General Hospital Following 25 repairs by the abdominal route the recurrence rate was 40 per cent the incidence following 37 operations by the thoracic route was only 14 per cent

The usual thoracic approach is the left postero lateral through the bed of the resected eighth or ninth rib the posterior end of an adjacent rib may be divided under cover of the erector spinae if further access is needed Even when the herniated stomach appears to lie in the right pleural cavity reduction and repair of the hernia is more readily achieved by the left transthoracic route owing to the easier access to the hiatus The lung is retracted upwards and forwards and the mediastinal pleura incised vertically down to the diaphragm it is not necessary to divide the pulmonary ligament The lower oesophagus and the herniated stomach are dissected free from the mediastinum and the ease of replacement of the cardia below the diaphragm is assessed The stomach is freed from the margins of the hiatus and from the under surface of the diaphragm in the region of the hiatus by stripping back the peritoneum The sac will probably be opened on the medial side of the hiatus where the peritoneum is more densely adherent to the sharp fibrous inner margin

Some authors recommend complete excision of the sac Sweet (1948) has developed a technique in which the sac is obliterated by multiple sutures Allison does not refer to excision of the sac as being of any great importance to the repair

At this stage Allison recommends a radial incision 2½ inches long in the dome of the diaphragm not encroaching upon or damaging the muscle fibres forming the hiatal ring through which a loop of tape is passed up through the hiatus and round the cardia traction on the tape facilitates reduction of the hernia and maintenance of reduction while the pleuro oesophageal ligament is repaired from below by suturing it to the under surface of the diaphragm The oesophagus is then displaced forwards and the crura are cleared permitting the anatomy of the posterior defect to be clearly appreciated The backward continuation of the crural fibres forming the lateral margins of the hiatus are then approximated behind the oesophagus by 1–2 carefully placed and loosely tied sutures of linen thread or silk it is most important that these sutures should not strangle the muscle fibres they encircle The fascia on the thoracic surface of the crura is also approximated to reinforce the posterior repair The tape is then removed the diaphragmatic incision sutured and the lung inflated by the anaesthetist An intercostal catheter is inserted into the

pleural cavity through one of the lower interspaces for attachment to a water seal and the thoracic incision is closed

The author has modified this technique in detail No incision is made through the diaphragm the reduction and repair being completed from above After freeing the stomach well back from the under surface of the diaphragm a series of 6–8 radially disposed mattress sutures of 60 gauge linen thread are passed through the diaphragm from above downward half an inch back from the margins of the hiatus pick up a loop of circular oesophageal muscle fibres above the cardia and then return through the diaphragm in the reverse direction When these sutures are loosely tied they have the effect of completely reducing the hernia obliterating the sac and firmly anchoring the cardia to the under surface of the diaphragm while preserving a substantial ring of diaphragmatic muscle round the lower oesophagus the fibres of this ring are not damaged by any encircling sutures The phrenic nerve is carefully preserved intact

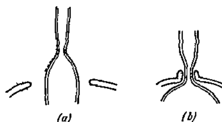


FIG 44 —Diagrams showing method of suturing the oesophagus above the cardia to the under surface of the diaphragm before the hiatus is repaired by approximating the crural fibres posteriorly

The crural fibres are then approximated behind the oesophagus by loosely tied thread sutures as described by Allison Three sutures are placed and the most posterior is tied first the third suture is not tied till the size of the hiatus has been estimated by digital examination and may be discarded if as often happens sufficient narrowing has been achieved by the first two sutures

Technique of resection

Following resection and restoration of bowel continuity by oesophago gastric anastomosis there is a risk of further reflux oesophagitis at a higher level as no technique for restoring a sphincter has yet been devised Experience has shown that the higher the anastomosis the less the risk of further oesophagitis It may be that the pressure of the aortic arch on the oesophagus prevents any reflux of gastric secretion gravity may play a part It has been suggested that the mucosa of the middle and upper thirds of the oesophagus is more resistant to the erosive action of gastric secretion but there is no definite evidence that this is so and as yet no satisfactory explanation has been found for the sudden cessation of ulceration at the junction of the lower and middle thirds in the untreated case of hernia with oesophagitis Perfusion experiments such as those performed by Ferguson might throw further light on this particular point

Allison has developed a technique for restoration of bowel continuity which completely eliminates any risk of further reflux oesophagitis The cardia is closed the stomach returned to the abdomen and the middle third of the oesophagus is

anastomosed to a loop of jejunum brought up into the chest thus relegating the stomach to the position of a back water a purely secretory organ playing no part in the transit of ingested food but still able to exert its anti anaemic effect

This operation however is not without its disadvantages It may be necessary to bring a long loop of jejunum up into the chest in order to perform an anastomosis and anatomical abnormalities of the blood supply to the upper jejunum or the not infrequent presence of sclerosis of the mesenteric vessels introduce the hazard of ischaemic necrosis of the bowel Some of the patients needing resection are small children and the mobilization of a jejunal loop without damage to the very *delicate mesentery and its vessels may be technically difficult* even in the most experienced hands Moreover Bain has recently shown that the physiological results of oesophago jejunal anastomosis following total gastrectomy are often less satisfactory from the patient s point of view than the clinician might hope intestinal hurry defective utilization of ingested fats and various manifestations of the dumping syndrome may cause the patient considerable distress but it is possible that some of these symptoms may be related more to the loss of the stomach than to the direct entry of ingested food into the jejunum

The author holds the view that preservation of some part of the stomach in continuity with the intestinal tract eliminates much of the discomfort that can follow an oesophago jejunal anastomosis and favours a combined resection of the stenosed segment of the oesophagus together with the fundus upper half of the body of the stomach and upper two thirds of the lesser curve followed by end to end anastomosis of the oesophagus and a tubular stomach constructed from the *remaining portion of the greater curve Following this operation the acid secretion* of the stomach had been permanently lowered below the normal level and re current ulceration of the remaining oesophagus has been observed only once in the cases followed up The patient has a restricted capacity for food for the first 6 months after operation and is advised to take frequent small meals his ability to accommodate a full meal then steadily returns to normal No other late complications have been observed in these cases This operation has been performed on 21 cases at Frenchay Hospital with 2 deaths A man of 59 years with chronic reflux oesophagitis and stenosis and chronic peptic ulceration of the stomach duodenum and jejunum succumbed after resection on the fifth post operative day from cardiac arrhythmia and failure a gastro enterostomy had been unpicked and a stenosed segment of jejunum resected 4 weeks previously A child of 4 years died on the seventh post operative day from a penicillin and streptomycin resistant staphylococcal lung infection Six other children on whom this procedure has been undertaken have had an uninterrupted convalescence and are now symptom free and feeding like normal children

A postero lateral incision is made and the left chest is entered through the bed of the sixth or seventh rib resected from the neck well forward as far as the cartilage The costal margin is not divided The oesophagus and herniated portion of the stomach are dissected from the mediastinum up to a level above the aortic arch There appears to be no risk of endangering the blood supply to the oesophagus The diaphragm is incised from the hiatus towards the anterior end of the chest wall incision and the stomach is mobilized by division of the left gastric artery close to its origin and the gastric splenic vessels and omentum The oesophagus is divided

above the stricture as close to the aortic arch as possible A point is then selected as far down the greater curve of the stomach as will reach without tension the stump of the oesophagus when the completely mobilized stomach is displaced upwards into the thorax At this point an incision is made into the greater curve of the stomach between Pringle narrow bladed clamps for a distance equal to the diameter of the divided oesophagus The division of the stomach is then continued obliquely downwards to a point two thirds of the way down the lesser curve from the cardia to the pylorus this part of the incision is then closed with two layers of continuous 40 gauge stainless steel wire sutures resulting in the formation of a tubular stomach with the upper end still occluded by a clamp The tubular stomach is then swung up into the thorax held approximated to the oesophageal stump and an end to end anastomosis performed in one layer using interrupted sutures of 40-gauge wire carefully placed through all layers The tendency of the oesophageal mucosa to retract upwards within the muscle coat is counteracted by traction on the mucosa during the anastomosis with fine Gillies hooks The anastomosis may need reinforcing where the vertical suture line in the stomach meets the line of the anastomosis No tension relieving or inverting sutures are inserted unless after careful inspection of the suture line any areas are observed where the blood supply to the tissues appears defective any such areas are infolded This technique for oesophago gastric anastomosis has been in use at Frenchay Hospital for 5 years with satisfactory results

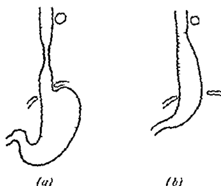


FIG 45 – Diagrams showing method of restoring continuity following oesophago gastric resection for chronic ulceration and secondary stenosis

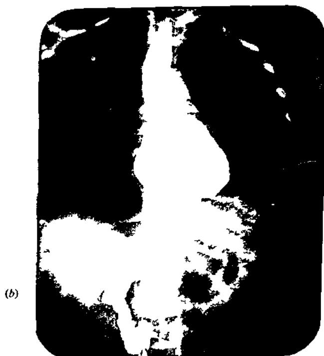
The completed anastomosis is allowed to retract upwards beneath the aortic arch The diaphragm is closed and sutured to the gastric tube which lies within in the mediastinum and does not encroach upon the left pleural cavity An intercostal catheter is inserted into the pleura for attachment to a water seal and the chest wall is repaired

Fluid balance is maintained for the first 24 hours after operation by an intra venous drip The patient is then allowed to take fluids by mouth on the second post operative day and can commence with soft solids on the fourth or fifth day For the first 6 months after operation the patient is advised to take frequent small meals till the capacity of the stomach increases sufficiently to accommodate a normal meal also to sleep propped up till the anastomosis has soundly healed



Fig 46.—Child aged 6 years Barium studies (*a*) before and (*b*) after oesophago gastric resection Note the anastomosis lying just beneath the aortic arch

(*a*)



(*b*)

and any bare areas caused by retraction of the oesophageal mucosa during the final stages of the anastomosis have had time to epithelialize

Conclusion

Henceforth there should be no excuse for omitting to consider hiatus hernia in the differential diagnosis in any patient with upper abdominal or oesophageal symptoms nor should the steps necessary to confirm or exclude its presence ever be omitted from the routine radiological examination of the upper gastro intestinal tract The oesophagoscope should be used more frequently by those clinicians trained to handle this indispensable diagnostic instrument

It is probable that the reported incidence of hiatus hernia will continue to increase for a while especially in children It is also probable that more cases of physiological disorder of the cardia unassociated by any demonstrable hernia will be discovered if every patient with symptoms referable to this area is fully investigated Much may be learnt concerning the influence of a hernia on gastric secretion and movements

In treatment the trend will probably be towards a freer use of surgery till such time as we have acquired sufficient experience to be able to offer a more accurate prognosis in any individual patient The clinician s approach to the problem of treatment will probably run the vacillating course that has been followed in the management of peptic ulceration of the duodenum during the last 30 years Certainly the focusing of attention on the condition should eliminate much human suffering and wastage of time and money on unnecessary treatment occasioned by inaccurate diagnosis The more frequent resort to early repair in patients suffering from Type I hernia should prevent the complications chiefly responsible for most of the symptoms and distress

CONGENITAL PLEUROPERITONEAL CANAL HERNIA

This type of hernia has been well described by numerous authors but certain aspects of the condition and its management deserve greater attention in the light of modern developments in diagnosis and surgical technique

Pathology

The defect is usually considered to be caused by failure of fusion of the three elements forming the diaphragm it is situated postero-laterally and is bounded on the chest wall side by a narrow shelf of diaphragmatic tissue the costal element The size of the defect varies within wide limits When the defect is due to congenital absence of the diaphragm partial or complete this lateral shelf of tissue is absent and the defect may involve the lateral margin of the hiatus which is then continuous with the gap in the diaphragm No hernial sac is present and there is free communication between the pleural and peritoneal cavities

In contrast to the hiatus hernia in this type the stomach is the least common of the viscera to be herniated into the chest most of the small intestine the proximal half of the colon and caecum part of the duodenum and the spleen are the organs commonly displaced above the diaphragm A part or the whole of the liver may also be present in the thorax

The hernia is commoner on the left side but right sided hernias are not as rare as some authors suggest Unfortunately the idea that herniation through the foramen of Bochdalek on the right side is rare has become so firmly established that it is normally undiagnosed when encountered often with dramatic and tragic results

Clinical picture

It is still probably true that more infants die of this condition during the first few days of life than are saved by surgical treatment In 1925 Hedblom stated that 75 per cent of all cases of congenital diaphragmatic hernia die before the age of one month The prognosis should have improved since then but it is nevertheless true that the diagnosis is still too often left to the morbid anatomist

The cause of death in infancy is usually pulmonary and cardiac embarrassment caused by the rapid increase in the bulk of the herniated intestine when feeding and the accompanying air swallowing Cyanosis and dyspnoea occur soon after birth and increase rapidly A diagnosis of pulmonary atelectasis is usually made but the gross displacement of the mediastinum towards the opposite side should suggest the correct diagnosis When extreme displacement is present the opposite lung may be partially collapsed and the resonance over the air containing bowel on the side of the hernia may indeed confuse the unwary Other signs of importance are the scaphoid abdomen due to the escape of its normal contents and the rapid variation in the cyanosis caused by the activity and changing distension of the herniated bowel



FIG 47 —Ten day old infant with hernia through a patent left pleuroperitoneal canal transthoracic repair performed on eleventh day of life on account of increasing cyanosis

Bowel sounds will only be audible over the chest if peristalsis is active and the absence of this sign is only significant if auscultation has been continued for many minutes If the bowel contains much fluid the signs are those of a pleural effusion and the displacement of the mediastinum may accelerate attempts at aspiration and the death of the infant from perforation of the herniated intestine Cases are on record where this sequence of events has occurred as in that described by Borrie

and Foreman (1948) Belsey and Apley (1949) have recorded two cases of right sided hernias where similar disasters were narrowly averted If the rule be adopted that no chest should be aspirated till after radiological examination this mistake may be avoided The signs may be those of a tension pneumothorax

If the infant survives the initial period of suffocation the clinical picture changes Symptoms of intermittent intestinal obstruction due to kinking or volvulus of the intestine may become more prominent but may vary with each attack depending upon the part of the bowel obstructed Not infrequently the duodenum is the site and signs of gastric dilatation may be detected if the obstruction is lower distension may again precipitate the symptoms and signs of suffocation

Some children survive untreated with bouts of low grade obstruction These children are usually undernourished and severe anaemia may be present resulting either from torsion vascular engorgement and haemorrhage or from the toxaemia attributed to closed loop obstruction by Cameron Watson and Witts (1950) Acute strangulation and gangrene of intestine may occur at any time

The symptoms may be relatively mild and the hernia may be discovered by chance when the chest is examined on account of some acute respiratory infection It is under these circumstances that the greatest risk of attempted aspiration occurs on the mistaken assumption of a pleural effusion The symptoms of intestinal obstruction may lead to an exploratory abdominal operation and confusion when the appendix cannot be located The diagnosis may be missed even during this procedure or ill advised attempts at reduction through an inadequate or ill placed incision may result in trauma to the intestine and subsequent ileus

Diagnosis

The first step toward diagnosis is an awareness of the condition Increasing or changing cyanosis in an infant or child with symptoms of intestinal obstruction associated with mediastinal shift should lead to consideration of the condition as one of the most likely causes acute respiratory embarrassment in a new born infant should prompt the same suspicion

Clinically the condition must be differentiated from other causes of mediastinal shift (a) atelectasis (b) spontaneous pneumothorax due to rupture of a cortical lung abscess (c) pleural effusion and (d) eventration of the diaphragm

The cyanosis alone may suggest pneumonia aspiration of vomit congenital atresia of the oesophagus or congenital heart disease

The diagnosis may be made on the basis of the physical signs already mentioned but can be confirmed only by radiological examination The skiagram changes are suggestive because of their very oddity they are typical of nothing The appearances of gas containing loops of intestine may be recognizable but the presence of much fluid in the bowel may obscure these changes The opacity is rarely as homogeneous as the shadow of a pleural effusion unless omentum alone has herniated The extent of the skiagram changes may vary considerably when the patient s position is changed from the erect to the head low position Multiple fluid levels may be seen Subsequent skiagrams taken by identical technique rarely show the same picture twice

Other cystic or air containing lesions must be differentiated by radiological interpretation (a) lung abscess or saccular bronchiectasis (b) loculated or



(a)

FIG 48 —Case of hernia through right pleurop ritoneal canal diagnosed as pleural effusion (a) Antero posterior skiagram (b) barium m al in same cas



(b)

encapsulated pleural effusion (c) pleural effusion with a broncho-pleural fistula (d) sub diaphragmatic abscess (e) interposition of colon between liver and diaphragm (f) other forms of diaphragmatic hernia for example hiatus hernia (g) dilatation or diverticula of the oesophagus (h) congenital cystic disease of the lungs (i) multiple tuberculous cavities (j) ruptured hydatid cysts and (k) tension pneumothorax

In none of these conditions does the skiagram vary from day to day as with a hernia An over penetrated film may show the contra lateral atelectasis and mediastinal shift more clearly than the bowel shadows and suggest that the atelectasis is primarily responsible

The diagnosis can be confirmed by a barium meal and a follow through will reveal how much of the intestine has herniated the position of the diaphragmatic defect may be shown but not its size

Prognosis

The infant usually dies within a few hours or days of birth from acute pulmonary embarrassment and suffocation If this phase is survived the patient may reach adult life with intermittent bouts of subacute intestinal obstruction accompanied by evidence of pulmonary compression but dramatic complications such as complete obstruction or strangulation may occur suddenly at any time and are usually fatal The overall prognosis in this condition is poor

Treatment

Indications for operation

Every case should be treated early by surgical reduction and repair in view of the lethal complications that can arise at any time With the onset of intestinal strangulation or increasing respiratory embarrassment operation becomes a matter of extreme urgency Many new born infants with congenital hernias could be salvaged by the prompt resort to surgery if the diagnosis is made before the infant is moribund With the help of an anaesthetist experienced in the problems of anaesthesia for thoracic surgery and in infancy major surgical procedures are tolerated surprisingly well in these poor risk cases

Early operation is also indicated to prevent the general maldevelopment that accompanies long standing disturbances of intestinal function Technically the sooner the operation is performed the easier will it be The longer the intestines are in the thorax the smaller relatively will the abdominal cavity become and the greater the difficulty experienced in replacing the abdominal contents within a peritoneal cavity inadequately developed to accommodate them Technical difficulty may be encountered at two stages of the operation (a) during reduction of the frequently dilated herniated intestines into the contracted abdominal cavity and (b) in attempting repair of very large defects

Surgical treatment should be planned in advance to meet these two eventualities

Technique of repair

As with the hiatus hernia two routes are available the abdominal and the thoracic Each has its advantages but the deciding factor will probably be the region with which the individual surgeon is better acquainted



(*a*)

FIG 48 —Case of hernia through right pleurop ritoneal canal diagnosed as pleural effusion (*a*) Antero-posterior skiagram (*b*) barium m al in same cas



(*b*)

When the abdominal approach is used difficulty may be encountered in with drawing the bowel from the pleural cavity due to adhesions to the lung or margins of the diaphragm or to the negative intrapleural pressure The use of force will be *followed by damage to mesenteric vessels or paralytic ileus A rubber catheter* passed upwards through the defect to allow air to enter the pleural cavity and neutralize the intrathoracic negative pressure while the bowel is reduced may assist at this stage All air must be aspirated from the pleural cavity following completion of the repair Only those cases where the defect is small enough to permit occlusion with an adequate overlap of the margins of the defect can be satisfactorily repaired from below Closure of the abdomen may be difficult even with complete muscular relaxation In some cases it may be advisable to make no attempt to repair the peritoneal and muscular layers merely suturing the skin the resulting abdominal hernia is then repaired at a later date

The advantages of the thoracic approach are that adhesions to surrounding structures can be divided under direct vision large diaphragmatic defects can be satisfactorily repaired and the problems of abdominal closure are avoided The chest is entered through the bed of the widely resected eighth or ninth rib The bowel is freed from the margins of the defect and reduced into the peritoneal cavity by gentle and patient compression Complete abdominal relaxation is essential during this phase of the operation A small defect i then closed by over lapping *its margins and suturing with two rows of mattress sutures of linen thread* or silk An intercostal catheter is inserted into the pleural cavity for attachment to a water seal the lung inflated by the anaesthetist—and this may be surprisingly easy despite compression from birth—and the chest wall repaired

Large defects not amenable to this method of repair are sometimes encountered Harrington (1948) has suggested mobilization of the attachments of the diaphragm by resection of the lower ribs in order to facilitate repair This method must lead to some deformity and impairment of thoracic function

Belsey has described a new technique for the repair of large defects The remnants of the diaphragm are detached all round from the costal margin the mediastinal attachment together with the nerve supply and much of the vascular supply is left intact The defect is then repaired by the overlapping technique The reduced but complete diaphragm thus constructed is then re attached to the chest wall at a level two interspaces above the normal level of attachment by interrupted mattress sutures of 36 gauge stainless steel wire Thus the communication between the thoracic and abdominal cavities is satisfactorily closed by a horizontal diaphragm rather than the normal dome shaped structure but retaining much of its normal muscular activity This technique by raising the level of the diaphragm results in a *relative* increase in the size of the *abdominal cavity and facilitates* reduction of the hernia whilst avoiding any deformity of the chest The functional results of this operation have been most satisfactory

REFERENCES

Allison P R (1948) *Thorax* 3 ?0

— (1951) *Surg Gynec Obstet* 92 419

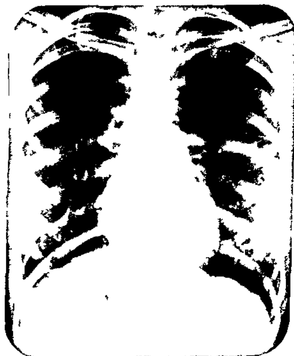
Andersen D H (1949) *Amer J Path* 25 163

Barrett N R (1950) *Brit J Surg* 38 175



FIG 49—Repair of large defect in right diaphragm by method described in the text (*a*) Before operation (*b*) 5 years after operation (*By courtesy of the British Medical Association*)

(*a*)



(*b*)

CHAPTER 8

CARDIOSPASM

GEOFFREY H WOOLER

CARDIOSPASM is not an isolated lesion of the cardia but is a disordered mechanism affecting the whole oesophagus The number of synonyms found in the literature—achalasia oesophagectasia idiopathic dilatation mega oesophagus neuropathic dilatation and phrenospasm—is in itself an indication of the wide diversity of opinion regarding the cause of this disease The term cardiospasm is used in this article in the belief that spasm of the cardia exists in the majority of patients and is frequently the first manifestation of the disease both clinically and radiologically

HISTORY OF CARDIOSPASM

Willis writing his *Pharmaceutica Rationalis* in 1672 described a certain man of Oxford a strong man and otherwise healthful enough labouring for a long time with often vomiting he was wont very often though not always presently to cast up whatsoever he had eaten Willis then made a sort of modified drain rod which he described I prepared an instrument for him like a rod of whale bone with a little round button of sponge fitted to the top of it the sick man having taken down meat and drink into his throat presently putting this (i e the rod) down in the oesophagus he did thrust down into the ventricle its orifice being opened the food which otherwise would have come back again and by this means he hath daily taken his substance for 15 years and doth yet use the same machine and is yet alive and well who would otherwise perish for want of food

Without doubt in this case the mouth of the stomach being always closed either by a tumour or palsie nothing could be admitted into the ventricle unless it were violently opened He was lucky not to p rforate the oesophagus and unfortunately this method of blind dilatation is still practised in many clinics today

Mikulicz in 1888 suggested that cardiospasm was due to spasm of the cardiac sphincter Einhorn published a paper in the same year about a case of marked dilatation of the oesophagus He suggested that it was due to a lack in the reflex relaxation or opening of the cardia during the act of swallowing This paper however seems to have been overlooked until 1896 when Rolleston presented a similar observation Hurst in 1913 propounded the same theory and on Sir Cooper Perry s suggestion the term achalasia (absence of relaxation) was introduced by him in 1914 Hurst also pointed out that a sphincter muscle differs from other muscles in having active relaxation as a part of its normal activity At rest its postural tone is sufficient to obliterate the lumen of the passage which it surrounds and in activity its relaxation opens the passage and removes the obstruction previously present Hurst believed that cardiospasm was due to paralysis of the vagal opening mechanism of the cardia

REFERENCES

Belsey R and Apley J (1949) *Arch Dis Childh* **24** 129
Borrie J and Foreman H M (1948) *Lancet* **2** 12
Brick I B and Amory H C (1950) *Arch Surg Chicago* **60** 1045
— (1949) *Miss Vall med J* **71** 2
Cameron D C Watson G M and Witts L J (1950) *Brit J Exp Path* **31** 349
Clerf L H Shallow T A Putney F J and Fry K E (1950) *J Amer med Assoc* **143** 169
Dunhill Sir T (1948) *British Surgical Practice* Vol 4 p 451 London Butterworths
Ernstene A C and McGurl F J (1940) *Cleveland Clin Quart* **7** 209
Ferguson D J Sanchez Palomera E Sako Y Clatworthy H W Toon R W and Wangensteen O H (1950) *Surgery* **28** 1022
Findlay L and Brown Kelly A (1931) *Proc R Soc Med* **24** 1561
Gilbert N C Day F L and Rall J E (1946) *J Amer med Assoc* **132** 132
— (1948) *M Clin N Amer* **32** 213
Guthrie D C and Avery Jones F (1940) *Annals Surg* **111** 971
Harrington S W (1948) *Surg Gynec Obstet* **86** 735
Hedblom C A (1925) *J Amer med Assoc* **85** 947
Mitchell R G (1950) Lancet **2** 236
Moersch H J (1938) *Ann Otol etc St Louis* **47** 754
Murphy W P (1942) *Bull New Engl Med Center* **4** 7
Nuzum F R (1947) *Amer Heart J* **33** 724
Ohler W R and Ritvo M (1943) *New Engl J Med* **229** 191
Pickhardt O C Rafsky H A Ghiselin F H (1950) *J Amer med Assoc* **142**, 310
Radloff F F and King R L (1947) *Gastroenterology* **9** 249
Rector L E and Connerley M L (1941) *Arch Path* **31** 285
Rigler L G and Eneboe J B (1935) *J Thorac Surg* **4** 262
— (1948) *J Amer med Assoc* **137** 1501
Ritchie J O and Winsauer H J (1947) *Amer J Med Sci* **214** 476
Ritvo M (1930) *J Amer med Assoc* **94** 15
St John F B Swenson P C and Harvey H D (1944) *Ann Surg* **119** 225
Schridde H (1904) *Virchows Arch* **175** 1
Shanks S C (1948) *Brit J Radiol* **21** 55
Sherman R S (1948) *J Amer M Womens A* **3** 136
Smithers D W (1950) *Brit J Radiol* **23** 261
Soresi A L (1919) *Ann Surg* **69** 254
Soutter L (1947) *Surg Clin N Amer* **27** 1121
Stapleton J G (1947) *Canad Med Ass J* **57** 13
Sweet R H (1948) *New Engl J Med* **238** 649
Taylor A L (1927) *J Path Bact* **30** 415
Wilkinson S A (1934) *New Engl J Med* **210** 1105

Tertiary waves also arise in the plain muscle segment They are small worm like contractions occurring when the oesophagus is distended lasting only a moment and if there are many of them the oesophagus has a corrugated appearance They are due to rings of contraction in the circular muscle of the oesophagus

Reversed peristalsis has also been described as occurring in the lower segments of the oesophagus This is probably not true for a wave of contraction passing down to the cardia naturally raises the level of retained barium if the fluid is unable to pass through into the stomach Thus the barium oscillating up and down the oesophagus gives this impression of reversed peristalsis

The control at the junction of oesophagus with the stomach

There are four different factors guarding the entrance into the stomach and preventing the regurgitation of stomach contents back into the oesophagus

The cardiac sphincter is the lower segment of the circular muscle of the oesophagus and plays only a small part in this mechanism

The pinch-cock action of the diaphragm The right crus of the diaphragm passes over to the left side and divides into two thick muscular pillars which grip the lower end of the oesophagus contracting during inspiration

The angle between the oesophagus and the stomach is of great importance for it produces a valvular opening As the stomach distends it increases this angulation and closes the opening into the oesophagus thus preventing regurgitation of gastric contents This factor explains why there is a free regurgitation with a sliding hiatal hernia but not with a paraoesophageal hernia

The oblique muscle fibres in the stomach wall augment the third factor They have a similar action to the pubo rectalis muscle of the anal canal for when they contract they too increase the angulation between the oesophagus and stomach

These four factors are of great importance when operating on the cardia and require particular attention in the treatment of cardiospasm

AETIOLOGY

The aetiology of the condition remains unknown and there are probably several factors contributing to the onset of the disease By far the most important is psychogenic trauma Psychiatrists contend that infants develop complexes soon after birth there would therefore appear to be no reason why cardiospasm should not occur at this early age following psychogenic trauma The youngest patient I have seen was a baby girl who commenced to vomit when she was weaned at 9 months She was an only child and even at this early age was obviously nervous and highly strung

There is no doubt that a strong psychological background is present when cardiospasm occurs in adolescence or in later life In such cases the cardia appears to be governed by emotion and goes into spasm with excitement

The following cases illustrate this point

Two patients developed dysphagia after their respective mothers had died of carcinoma of the oesophagus A farm labourer started to have dysphagia after he had been knocked down by a horse Another patient presented herself with cardiospasm soon after her father had died it was relieved by the Negus dilator and she was well until her mother died when all her symptoms returned and she required further treatment

In 1922 Mosher concluded that cardiospasm was due to some deformity of the liver tunnel He wrote as follows In watching a patient with a normal oesophagus swallow the barium is seen to come to a point momentarily at the upper border of the liver then after a delay of a second or two the liver tunnel opens up and the barium streams into the stomach In the same year Chevalier Jackson wrote that the diaphragmatic pinch cock and kinking of the oesophagus were the normal mechanisms by which the food in the stomach was prevented from regurgitation He suggested that it was a failure of the pinch cock to relax that produced the stenosis and the so called cardiospasm

In 1925 Walton defined cardiospasm as a dilatation and hypertrophy of the oesophagus in which at post mortem examination no obstruction can be found distal to the dilatation It appeared that the obstruction which was present during life had ceased to function after death Walton stated that there was a spasm of the part for which he suggested a congenital origin

In 1926 and 1927 Rake reported on the microscopical findings of three cases of cardiospasm Previous observers had been paying particular attention to the degree of muscular hypertrophy of the oesophagus in the vicinity of the cardia but they had disregarded the condition of the nerve fibres and cells Rake demonstrated an inflammatory reaction in and around the ganglia and connecting nerves of Auerbach s plexus and he showed that in the later stages this produced fibrosis of the ganglia and complete disintegration of the ganglion cells He believed that the cause of cardiospasm was a progressive degeneration of Auerbach s plexus These findings have been confirmed by Gallinaro (1947) working with Valdoni in Rome However I believe that the degeneration of Auerbach s plexus is secondary to dilatation of the oesophagus and that it is not the cause of cardiospasm

ANATOMY AND MOVEMENTS OF THE OESOPHAGUS

The oesophagus is divided into two segments The upper segment comprises the proximal third lying above the aortic arch Its wall is composed of striped muscle supplied by the recurrent laryngeal nerves The lower segment comprises the distal two thirds lying below the aorta its wall is of plain muscle supplied by the vagal plexus The nerve fibres supplying these two segments of the oesophagus originate from different nuclei in the medulla and control the movements of the oesophagus which are different in the two segments

There are 3 forms of oesophageal contractions primary secondary and tertiary The primary wave is initiated by the act of swallowing it begins in the upper third of the oesophagus and proceeds in an unbroken manner down to the cardia As it passes downwards the oesophagus above the advancing wave remains in a state of contraction Von Brucke and Satake (1913) studying oesophageal action currents concluded that the primary wave was an advancing tetanic contraction

The secondary wave originates in the region of the aortic arch and is confined to the plain muscle segment It is initiated by the presence of food in this part of the oesophagus and is of a similar nature to the primary wave consisting of a band of contraction passing down to the cardia McLaren (1943) showed by kymography that these waves were not preceded by waves of relaxation and so were not the same as true peristalsis in other parts of the intestinal canal

Dr Soler Roig of Barcelona in a personal communication stressed the importance of psychotherapy in cardiospasm The disease is extremely common in Spain and many of his patients are cured by this therapy alone Such results have not been obtained in Great Britain In my experience the lesion appears to be organic and is not cured by psychotherapy

Allison has had two cases of cardiospasm occurring in old age after cerebral vascular lesions It therefore seems probable that there is a centre in the brain controlling the movements of the oesophagus and the tone of the cardiac sphincter

Example A woman aged 62 years suffering from polycythaemia vera developed a severe headache and weakness in her left leg. At the same time she noticed that he was unable to swallow Radiologically and at oesophagoscopy she showed the typical appearance of cardiospasm Her dysphagia was relieved by treatment with the Negus hydrostatic dilator

No case in this series was associated with other neuro-muscular disorder such as megacolon One had duodenal ileus two had gastric ulcers and one had a paraoesophageal hernia These were thought to be incidental findings in no way connected with the disease

A condition similar to cardiospasm sometimes occurs following vagotomy Rob demonstrated this complication in 1947 since when I have seen two cases The dysphagia is of a transient nature coming on about 3 days after vagotomy and lasting for a week or so before it gradually disappears Radiologically there is a constriction at the lower end of the oesophagus in the region of the cardia Proximal to the constriction the oesophagus is dilated and inactive There appears to be no increased activity to overcome the constriction

PATHOLOGY

The obstruction in cardiospasm is in the segment of the oesophagus lying within the diaphragmatic tunnel This segment is about 3 centimetres in length and includes at its lower limit the cardiac opening into the stomach The muscle wall of this segment is not hypertrophied but at operation it is felt to be firm as though in a state of contraction No adhesions inflammation or bands surround it and it is frequently the most normal looking part of the oesophagus

The pinchcock action of the diaphragm and the so-called liver tunnel have nothing to do with the disease In this series one patient had a large paraoesophageal hernia as well as cardiospasm and another patient (Fig 50) had such a large hiatus through the diaphragm that the cardia and lower oesophagus prolapsed into the abdomen Both these patients required Heller s operation and their oesophageal hiatuses were repaired at the same time

The oesophagus proximal to the contracted segment quickly enlarges Its lumen becomes wider and its wall thickens Both the circular and longitudinal muscular layers are hypertrophied increasing in size as the oesophagus dilates The mucosa becomes oedematous and ulcerated

The greatly enlarged lengthened and tortuous oesophagus pushes the trachea forwards and in the centre of the chest swings over to the right side because there is no room for it on the left—the aorta is in the way When it reaches the diaphragm it takes a right angled bend to the left passes behind the heart and through the diaphragm to join the stomach (Fig. 51)



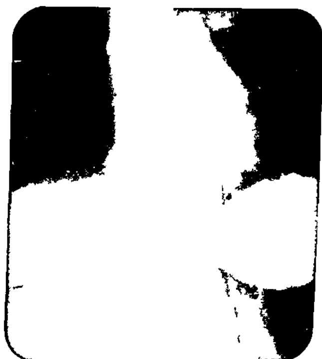


FIG 50 —(*a*) Prolapse of the cardia and lower oesophagus through the hiatus into the abdomen (*b*) same case after Heller s operation reduction of the prolapse and repair of the hiatus

feel the oesophagus go into spasm when they are excited and they can feel it relax after taking a hot drink The first few mouthfuls of food may cause little dis comfort but further swallowing produces the sensation that food is sticking behind the lower third of the sternum If they continue to eat fast food regurgitates into the pharynx These symptoms may fluctuate from day to day but on the whole they gradually worsen as the disease progresses Anything other than the normal daily routine may bring on an attack It was interesting to notice that the patients who had not been relieved completely by treatment felt very much worse when they received my letter asking them to report again to hospital for review

The barium swallow is of supreme importance in assisting the diagnosis and in understanding the natural course of the disease Radiographs alone may be mis leading because important factors in the diagnosis are o sophageal movements and the time taken for barium to pass through the cardia neither of which can be portrayed on a radiograph

When an early case is screened the first 1 or 2 mouthfuls of barium are seen to pass readily into the stomach The oesophagus apart from showing increased movement in the lower two thirds presents no abnormality and is not dilated As the patient continues to swallow barium a constriction about 1-2 centimetres long appears at the lower end of the oesophagus This constriction involves the cardia and the cardiac ampulla or that part of the oesophagus lying in and below the diaphragmatic hiatus If one continues to watch for a few minutes the spasm at the lower end becomes more noticeable Barium is retained in the oesophagus which begins to dilate in order to accommodate it The retained barium stimulates oesophageal movements Secondary waves increase in size and rapidity as the oesophagus dilates until it looks alive with excitement It appears to be fighting as hard as it can to push barium through into the stomach This activity may continue for half an hour or more until the oesophagus is empty If the patient is given a drink of hot water it often relaxes the cardia and clears the oesophagus in a few minutes

The stage of activity which I have just described lasts for months The oesophagus then tires of its increased effort and becomes passively dilated This occurs in the second stage when most patients present themselves for treatment

Second stage—During the second stage dysphagia and sternal discomfort after swallowing grow in severity Patients try to combat these symptoms by eating slowly choosing their diet carefully and washing solids down with fluids A few patients learn the trick of hyperextending their back after meals which straightens out their tortuous oesophagus increases the gravimetric pressure and so facilitates the contents to pass into the stomach The enormous o sophagus of a few patients may act as a drip feed and prevent wasting but usually they lose weight rapidly because they are afraid to eat They suffer from avitaminosis become thin and anaemic and may present in a severe degree of cachexia If the cricopharyngeus is not functioning properly they have regurgitation of food into the pharynx at night

Complications

Cardiospasm sometimes causes certain complications which may be the pre senting symptoms

The degeneration of Auerbach s plexus has already been mentioned This commences at the lower end of the oesophagus and gradually proceeds up in the same way as oesophageal movements cease Sometimes after treatment normal movements never return to the lower segment in which case it is reasonable to presume that there has been permanent damage to the nerve cells

If the oesophageal hiatus is weak the greatly enlarged and loaded oesophagus may prolapse through into the abdomen as shown (Fig 50) Usually the oesophagus kinks to the right and so the right diaphragm bears most of the weight but if this does not occur the oesophagus may prolapse through into the abdomen



Fig 51 —The oesophagus when it reaches the diaphragm takes a right angled bend to the left

Age and sex incidence

Cardiospasm affects people of any age The youngest of the patients reviewed in this paper commenced to vomit when she was 9 months old the oldest 73 years The usual age for the disease to manifest itself is during the third decade In this series it occurred twice as commonly in women as in men

Course of the disease

Johnstone s radiological findings are included with my own clinical observations

Cardiospasm affects the whole of the lower segment of the oesophagus It runs a continuous slow progressive course which may be divided into two stages The first is of greatly increased activity of the oesophagus the second is the gradual cessation of all activity followed by passive dilatation

First stage —Patients in the first stage are oesophagus conscious They can



FIG 53—Lung compli cations case No 2 Chronic inhalation pneumonia producing bilat ral pulmonary fibrosis and bronchiec tasis



FIG 54—Lung complications case No 3 Paraffin pneumonia occurring in a patient with ca diospasm who took liquid paraffin to lubricate her alimentary canal

Lung complications

Atelectasis —A girl aged 16 years gave a two months history of cough and sputum dyspnoea and two haemoptyses Radiography showed collapse of the right lower lobe caused by pressure on the right bronchial tree It was only after close questioning that a history of dysphagia could be obtained This had developed at the age of 10 when she was too young to appreciate her condition Her mother thought she had merely gone off her food During the subsequent 5 years the oesophagus gradually dilated eventually compressing the right lung Enlargement of the oesophagus to the left was prevented by the aortic arch and the descending aorta (Fig 52)

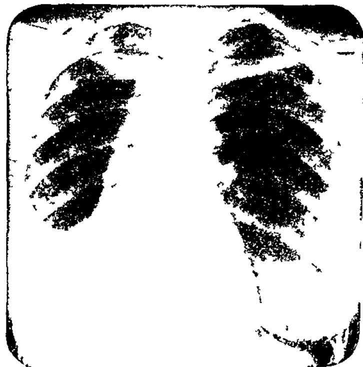


FIG 52—Lung complications case No 1 atelectasis The dilated oesophagus is seen encroaching on the right lung field producing widening of the superior mediastinum and there is collapse of the right lower lobe The lobe re-expanded fully 24 hours after the cardia had been dilated with the Negus hydrostatic dilator

Pneumonitis and bronchiectasis —A girl aged 18 years presented as a typical case of bronchiectasis She gave a history of pneumonia 5 years previously and as a result she developed a cough which had persisted Attacks of bronchitis had recurred each winter and one week before her first attendance she had a small haemoptysis She gave no history of dysphagia there was nothing in her symptoms to suggest that she had cardiospasm Her chest radiographs however showed cardiospasm and bilateral bronchiectasis which was probably due to a chronic inhalation pneumonia caused by food which had regurgitated from the oesophagus (Fig 53) Belcher (1949) has described similar pulmonary complications which he styles as dysphagia pneumonitis

Paraffin pneumonia—The third lung complication occurred in a woman

advanced cardiospasm and had recently developed a post cricoid carcinoma It is reasonable to presume that this arose from a pharyngeal web caused by the secondary anaemia

DIAGNOSIS

The diagnosis is usually established by radiology Oesophagoscopy should be carried out in all cases to confirm the diagnosis and also for the introduction of therapeutic measures

Oesophagoscopy

When the barium swallow shows a dilated oesophagus with food retention oesophagoscopy may be carried out safely under general anaesthesia provided the patient is adequately prepared beforehand This may entail having only a fluid diet for 2–3 days—then just prior to the examination a large stomach tube is passed into the oseophagus which is thoroughly washed out with warm dilute sodium bicarbonate solution Food debris may still remain in the oesophagus so when the general anaesthetic is commenced it is advisable to have the oesophagoscope in readiness and to watch the pharynx for regurgitation of food A second and a third suction tube should be available in case one becomes blocked with food debris Under general anaesthesia when the cough reflex is abolished food regurgitating into the pharynx may quickly be inhaled It is absolutely essential to avoid this If the oesophagus is greatly dilated it may contain foul smelling fluid due to bacterial decomposition The oesophageal mucosa may be inflamed and show gross ulceration which is in part due to stagnation and decomposition of its contents and in part due to pressure necrosis caused by the weight of retained food in the lumen It is the lower horizontal part of the oesophagus running behind the heart to the hiatus which bears the full weight of the contents and is consequently the first to ulcerate

After the oesophagus has been cleansed the cardia may be difficult to find for the adult Negus oesophagoscope will not reach to the cardia of a greatly lengthened and kinked oesophagus it lies around the bend to the left When the oesophagus is greatly lengthened it is necessary to use the 50 centimetres long oesophagoscope The technique of dilating the cardia will be described later When this has been carried out the stomach contents regurgitate back into the oesophagus The oesophagoscope may then be passed through into the stomach

Differential diagnosis of cardiospasm

In children there is no other condition which produces radiological appearances similar to those of cardiospasm For completeness I should like to mention two other causes of dysphagia occurring at an early age

(*a*) The so called congenital stenosis is most probably a short oesophagus with part of the stomach lying in the chest the stenosis being due to peptic ulceration of the oesophagus It may appear as a sharply defined narrow stricture with smooth margins or it may be irregular

(*b*) Simple stricture following the accidental drinking of a corrosive substance occurs in children The site at which this usually develops is 2–3 inches above the diaphragm This is probably due to the fluid being held up here momentarily by muscular spasm

aged 31 years who had been in the habit of taking liquid paraffin after every meal because she believed that it lubricated her alimentary tract allowing food to glide into the stomach The paraffin being of low density floated on the top of the liquid content of her oesophagus She also found eating such a nervous strain that she had to lie down after every meal Small amounts of liquid paraffin then regurgitated into her pharynx which she inhaled causing a paraffin pneumonia (Fig 54)

Rheumatic complications

Toxic arthritis—A woman aged 42 years stated that her joints had been swollen for 2 months the interphalangeal knee and elbow joints being mostly affected When questioned she gave a 15 years history of dysphagia which commenced after her first pregnancy She had an enormously dilated oesophagus the contents of which smelt as bad as a pelvic abscess The lower third of the oesophagus was found to be grossly inflamed and ulcerated

The arthritic condition was probably due to toxic absorption from the ulcerated oesophagus for after the oesophagus had been washed out and the cardiospasm relieved by dilatation her joint symptoms dramatically cleared up overnight The relief however was only temporary and when the spasm returned her joints swelled up again The patient in fact was able to tell the condition of her cardia merely by inspecting her joints

Rheumatoid arthritis—A woman aged 32 years presented as a case of rheumatoid arthritis with swelling of her hands knees and elbows The condition of her joints cleared up just as effectively as in the previous patient after the cardiospasm had been relieved One man aged 36 years had both rheumatic and lung complications and had had cardiospasm since he was a child he did not know what it was like to be able to swallow properly and did not complain of dysphagia until his attention was drawn to his oesophagus For 20 years he had had rheumatism and for 6 years recurrent attacks of pneumonitis first in one lung and then in the other These inflammatory episodes in the lungs were watched radiologically and were not thought to be due to an inhalation pneumonia—until one day the dilated oesophagus was seen encroaching on the right lung field A barium swallow and oesophagoscopy confirmed the condition of cardiospasm and elucidating his history very carefully later he had certainly had cardiospasm since he was a child

Relation to carcinoma

Carcinoma is a very rare complication of cardiospasm but has been found arising in the dilated oesophageal wall Much more frequently however carcinoma arises in the fundus of the stomach or the lower end of the oesophagus and produces oesophageal dilatation which radiologically may be mistaken for cardiospasm

One patient had had cardiospasm for 40 years which had been treated unsuccessfully with mercury bougies She presented herself because her dysphagia had increased during the previous 3 months On examination she was found to be grossly wasted and anaemic her oesophagus was enormous and atonic She had

Late in life carcinoma is the most important lesion to consider in the differential diagnosis especially when the history is not typical of cardiospasm and the symptoms are of recent onset (Fig 55) It may be impossible to decide radiologically the true nature of the condition—for a high carcinoma of the stomach can spread submucously around the cardia producing obstruction and the appearance of cardiospasm Oesophagoscopy reveals no ulceration for the growth is deep to the mucosa—but on passing a bougie the cardia feels hard and fixed The constriction is tighter than a cardiospasm

None of these investigations is necessarily conclusive and in such circumstances the only course is to explore the area of the stenosis

Simple spasm of the oesophagus does occur but is extremely rare Only one case has been recorded in this clinic This was a man aged 4? years who gave a 12 years history of attacks of dysphagia coming on when he worked overtime The attacks lasted 2–3 days (Fig 56) Oesophagoscopy showed that the whole of the oesophagus below the bifurcation of the trachea was in spasm the mucous membrane being quite normal He was relieved of his symptoms by the passing of the oesophagoscope which dilated the lower segment He has not required further treatment

Johnstone (1950) has demonstrated the radiological features occurring with aortic atheroma which may be mistaken for cardiospasm His theory is that the tortuous and kinked lower thoracic aorta stimulates the vagal plexus and produces a small contracted vagotonic stomach The oesophagus dilates and accommodates most of the barium when it is swallowed The lumen through the cardia appears to be small but there is no delay in the passing of barium This condition is described by him in another section of this book

TREATMENT OF CARDIOSPASM

Innumerable different ways of treating cardiospasm have been described but the best methods still remain as dilatation with Negus hydrostatic dilator and Heller s operation

The treatment may be divided into

Medical—Psychiatric—advice by an expert psychologist anti spasmodic drugs —such as octylnitrite or amylnitrite given before meals light diet and washing down all solid food with a hot drink after meals

Dilatation with the Negus hydrostatic bag—Other dilators which the patients are taught to pass themselves activate the swallowing phobia and never cure the condition of cardiospasm

The Negus hydrostatic bag is used in the following way The oesophagoscope is passed under general anaesthesia After cleansing the oesophagus the cardia is sought This is dilated with gum elastic bougies up to size 30 The stilette of the dilator is then passed through the cardia and the Negus hydrostatic dilator is inserted over the stilette It is important that the constricted part of the oesophagus should be in the centre of the Negus bag when the latter is distended by injecting 20–40 cubic centimetres of water Otherwise the bag slips up or down thus failing to dilate the constriction It is difficult however to be certain that the bag lies in the centre of the constriction In order that the dilatation shall be complete the bag should be distended 3 or more times at varying distances from



FIG 55—Differential diagnosis Carcinoma of the cardia in a man aged 62 years Prior to admission he had been treated as a case of cardiospasm by swallowing mercury bougies



FIG 56—Differential diagnosis Simple spasm of the oesophagus which was completely relieved by oesophagoscopy

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TREATMENT OF CARDIOSPASM

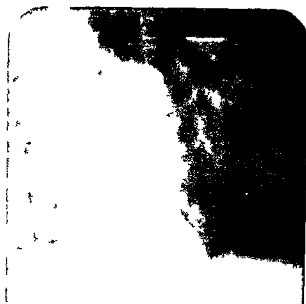
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(*a*)



(*b*)

FIG 57 —Treatment of cardiospasm with the Negus hydrostatic bag (*a*) before treatment (*b*) after one dilatation

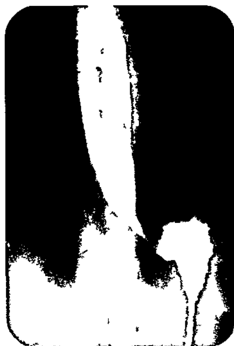


FIG 58 —Treatment of cardiospasm with the Negus hydrostatic bag (*a*) before treatment (*b*) 14 months after treatment showing return of oesophageal movements and diminution in size of the oesophagus

(*a*)



(*b*)

the incisor teeth This method of treatment has given excellent results in 80 per cent of patients The remaining 20 per cent have had Heller s operation (Figs 59 and 60)

Surgical—Before operating on the lower oesophagus and the cardia it is advisable to recall the mechanism in this region for to destroy all factors preventing regurgitation of gastric contents produces a severe oesophagitis peptic ulceration of the oesophagus and haemorrhage—from which people have died The operations of cardioplasty, oesophagoplasty and oesophagogastrostomy for the treatment of cardiospasm should be condemned They are killing operations which relieve the dysphagia for a few months and then produce the most sever oesophagitis with subsequent peptic ulceration In such circumstances when these unfortunate operations have been performed the only escape for the patient s resection of the ulcerated segment and oesophagojejunostomy following the method of Roux

Extra mucous cardiomyotomy or a modification of Heller s operation is the only safe surgical procedure for cardiospasm It has given excellent results and all the patients so treated in this clinic have had no oesophageal reflex post operatively

Technique of cardiomyotomy

Heller first performed this operation on 14 April 1913 in Leipzig He intended to do an oesophagogastrostomy for a case of cardiospasm but found the oeso phageal wall so degenerate and friable that it was not possible Instead using an abdominal approach he incised all the muscle fibres longitudinally twice on the front and back of the oesophagus down to mucosa He admitted that it was not his original idea but had obtained it in 1901 from Gottstein who speaking about extra mucosal pyloroplasty for congenital pyloric stenosis stated that this operation could be applied to the cardia Heller s first case did so well that he continued to employ this method The modern operation differs from the original in two ways *for only one incision through all muscle fibres is used and the incision is* longer than Heller employed It is an advantage to carry it down through gastric muscle and up well on to the dilated part of the oesophagus and it is more safely and more easily performed by thoracotomy

Pre operative treatment

The patient is given a high protein fluid diet for a few days prior to the operation

All septic teeth have already been removed at the first oesophagoscopic examination and a skiagram of the chest has been taken to exclude pulmonary complications

A physiotherapist visits the patient twice daily in order to teach breathing exercises and gain the confidence of the patient

The oesophagus is washed out once or twice before operation depending upon the size of the oesophagus and the quantity of retained food A large sized stomach tube is used for this procedure the last wash out being given just before operation

500 000 units penicillin twice daily intramuscularly are given the day before operation

The operation

Immediately after induction of anaesthesia the patient is oesophagoscoped and all food debris removed from the oesophagus This is the only safe and sure way of cleansing the oesophagus—wash outs with rubber tubes are frequently useless but they do help a little and this is why they are still employed pre operatively When the oesophagus is clean (and I have spent half an hour cleaning then sometimes (two Tampax packs are inserted below the cricopharyngeus through the oesophagoscope These packs help to prevent regurgitation of gastric contents into the pharynx during the operation

The operation is conducted in the right lateral position The left eighth rib is resected the left pleural cavity opened and the mediastinal pleura incised behind the lateral pulmonary ligament The oesophagus is mobilized and secured with a tape

The whole pathology can be seen in the chest for normally no part of the oesophagus lies within the abdomen The narrowed segment is freed from the hiatus and the entrance of oesophagus into the stomach can then be seen An incision about 4 inches long is made through the contracted segment extended upwards on to the dilated part of the oesophagus and downwards through gastric muscle The incision is placed on the antero-lateral aspect of the oesophagus and is made through all muscle fibres care must be exercised not to open the mucosa and if this unfortunately does happen the hole should be closed by suturing transversely in order not to constrict the lumen

When all muscle fibres have been divided the mucosa herniates through the incision No attempt is made to cover the mucosa The chest wall is closed around an underwater drainage tube which is removed the following day The Tampax packs are removed from the upper end of the oesophagus when the patient has been turned into the supine position

Post-operative treatment

The patients are nursed well propped up with pillows Daily breathing exer cises and intramuscular penicillin are continued Only fluids are given by mouth for the first 3 days after operation the diet is then gradually increased until by the ninth day they are taking ordinary food As a general rule they are allowed out of bed on the third day and are discharged from hospital 9–12 days after operation

The post operative barium swallow shows no delay at the cardia (Fig 59) oesophageal movements come back and the lumen again returns to a normal size The diminution in size may take about a month depending upon how large the oesophagus was before operation The very large atonic oesophagus becomes much smaller and may never recover completely except in children Fig 60 is an example of excellent recovery in a child of 2 years whose oesophagus was of the large atonic type

SUMMARY

The cause of cardiospasm is unknown Psychogenic trauma is an important factor in initiating its onset

It occurs in patients of any age They may not complain of dysphagia but of the complications which are commonly pneumonitis and rheumatoid arthritis



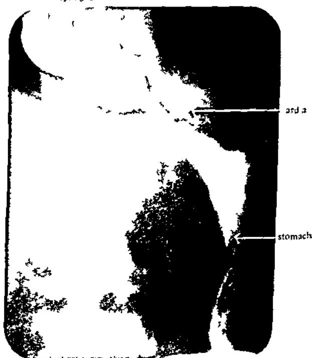
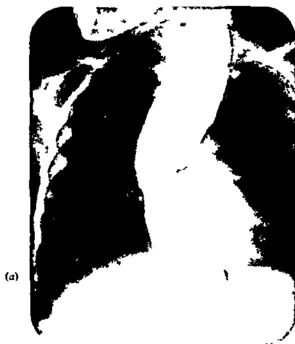


Fig 59—Treatment of cardiospasm with a *modified Heller's operation* (*a*) before treatment showing the greatly dilated and atonic oesophagus with a small diverticulum into the mediastinum presumably due to the oesophageal wall becoming adherent to a mediastinal gland (*b*) after Heller's operation showing the return of oesophageal movements and the wide lumen through the cardia into the stomach



(*a*)



(*b*)

FIG 60—Treatment of cardiospasm with a modified Heller s operation (*a*) before treatment child ac d 2 years 9 months with a laree atonic oesophaeus (*b*) after Heller s operation showing return of the oesophagus to a normal size

With the Negus hydrostatic bag 80 per cent of patients have been cured by dilatation the remaining 20 per cent h ve had Heller s operation When op rating upon this condition the importance of not destroying all the mechanisms at the cardia is stressed

REFERENCES

Allison P R Johnstone A S and Royce C B (1943) *J Thorac Surg* 12 432
Alvarez W C (1939) *An Introduction to Gastro Enterology* London Heinemann
Barlow D (1942) *Brit J Surg* 29 415
Belcher J R (1949) *Thorax* 4/1 44
Brown Kelly A (1919) *J Laryng* 34 289
Brucke E T Von and Satake J (1913) *Pflug Arch ges Physiol* 150 .08
Carlson A J Quoted by Templeton
Dick R C S and Hurst A F (1942) *Quart J Med* 11 105
Einhorn Max (1888) *Med Rec N Y* 34 751
Findlay L (1933) *Thomson s Clinical Study and Treatment of Sick Children* Edinburgh Oliver and Boyd
— and Kelly A B (1931) *J Laryng* 46 797
Gallinaro E A (1947) *Rass Neurol Veg* 4/6 464
Hacker V Von and Lotheissen G (1926) Chirurgie der Speiserohne *Neue dtsch Chir* 34 292
Harrington S W (1943) *Amer J Roentgenol* 49/2 185
Heller E (1913) *Mitt Grenzgeb Med Chir* 57 141
— (1921) *Ver dtsch Ges Chir* 45 144
Hurst A F (1913) *Proc R Soc Med* 7 150
— (1914) *Ibid* 8 22
— (1934) *J Amer med Ass* 102 582
Jackson Chevalier (1922) *Laryngoscope St Louis* 32 139
Johnstone A S (1941) *Brit J Radiol* 14 177
— (1943) *Ibid* 16 192 357
— (1946) *Ibid* 19 219 101
— (1946) *Edinb med J* 53 160
— (1950) *Textbook of X ray Diagnosis* part I sect 2 page 65 Ed by S Cockrane Shanks and P Kerley London Lewis
— and Wooler G H (1950) *Postgrad med J* 25 203
Knight G C (1935) *Brit J Surg* 22 155
Lambert A V S (1913) *Ann Surg* 58 415
Lendrum F C (1937) *Arch intern Med* 59 475
Maingot R (1944) *Postgrad med J* 20 278
McLaren J W (1943) *Brit J Radiol* 16 270
Mikulicz J Von (1904) *Dtsch med Wschr* 30 17
Mosher H P (1922) *Laryngoscope St Louis* 32 238
Ochsner A and De Bakey M (1940) *Arch Surg Chicago* 41 1146
Paterson D R (1919) *J Laryng* 34 285
Rake G W (1926) *Guy s Hospital Rep* 76 145
— (1927) *Ibid* 77 141
Rolleston H (1896) *Trans Path Soc London* 47 37
Royal Soc of Medicine Proceedings of (June 1950) 43/6 4.1 (Se tion of Surgery pp 13–26)
Schatzki R Quoted by Templeton
Templeton F E (1944) *X ray Examination of the Stomach* Chicago Univ Chicago Press
Teschendorf W Quoted by Templeton
Vinson P P (1922) *Minne Med* 5 107
Waldrenstrom J and Kjellberg S R (1939) *Acta Radiol Stockh* 20 618
Walton A J (1925) *Brit J Surg* 12 701
Willis Thomas (1672) *Pharmaceutica Rationalis*
Wooler G H (1948) *Thorax* 3/2 53

CHAPTER 9

CARCINOMA OF THE OESOPHAGUS

IVOR LEWIS

THE present phase of the surgery of the oesophagus begins in 1938 This was the date of two notable achievements (1) three consecutive recoveries from the Torek operation by Garlock (1938) and (2) Adams and Phemister s (1938) first case of transthoracic oesophagectomy with immediate oesophago gastric anastomosis for cancer of the lower end of the oesophagus The first report showed that resection of the oesophagus was about to become a project of routine feasibility the second broke entirely new ground by freely opening both chest and abdomen throwing them into one in order to secure anastomosis without tension and thus obtain perfect palliation as well as the prospect of cure

The two principles of free transpleural resection and immediate restoration of continuity have governed the rapid development in the last few years Adams and Phemister s operation became the prototype procedure for cancer of the lower end and seems likely to remain so although the recent adoption of the abdomino thoracic incision for it has much improved the approach By 1944 the two principles had been extended to cancer of the mid oesophagus either using a left thoracotomy (Sweet 1944) or a right thoracotomy in Great Britain It thus came about that the Torek oesophagectomy with its gastrostomy and cervical oesophagostomy was entirely given up

With increasing experience the mortality fell—from about 90 per cent before 1938 to 50 per cent by 1944 and to 30 per cent and even less at the present time

AETIOLOGY

Most cases of cancer of the oesophagus occur between 55 and 75 years of age post cricoid carcinoma often in younger people—usually women The disease is five times commoner in men adding together all the sites

The sites are suggestive apparently those of maximum irritation that is all that can be said It is of interest that Benciolini (1930) found that at these sites the mucosa of normal gullets occasionally shows thickening and round celled infiltration It is said that the incidence in the liquor trades is considerably higher than the average barmen for example having an incidence four times higher than the average Hot drinks spices septic teeth have likewise been blamed

Cases are certainly met which have developed on stricture spasm or leucoplakia Cancer has also been described arising in a diverticulum in a benign polyp and at the site of a revolver bullet buried for 40 years in the oesophagus wall! The frequent relation of the Plummer Vinson or Paterson dysphagia to post cricoid cancer is well recognized

MORBID ANATOMY

There are three common sites for cancer of the oesophagus cervical and supra aortic 20 per cent middle 40 per cent and lower 40 per cent

Histologically there are two kinds—squamous carcinoma and adenocarcinoma The squamous is the form arising at all points except the cardia where the cancer is usually an adenocarcinoma arising from gastric mucosa in the opening Moreover cancers originating in the stomach itself often encroach on the cardia Does adenocarcinoma occur in the oesophagus above the cardia? Garlock (1942) with his vast experience, states that if on oesophagoscopy and biopsy a growth of

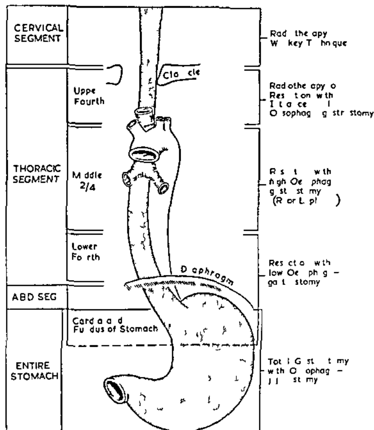


FIG 61—Diagrammatic representation of the sites of cancer in the oesophagus *and cardia with the* treatment of choice at the present time 1951 Modified from Sweet (*By courtesy of G T Pack and C V Mosby Co*)

the oesophagus is found to be an adenocarcinoma then that growth no matter at what level met with has originated at the cardia and spread upwards In a recent note Carrie (*1950*) *reports what he claims to be the second authentic* case of adenocarcinoma of the upper part of the oesophagus His remark is worth quoting Adenocarcinoma of the upper end of the oesophagus has become somewhat like a unicorn for while the authors of most books state that this tumour does occur they do not say that they have seen it themselves and fail to say who did Although it be admitted that adenocarcinoma of the oesophagus

does occur as a curiosity it is still not necessary to postulate that it arises in ectopic gastric mucosa In the oesophagus there are oesophageal glands which may coalesce into small patches especially in the cervical region these admittedly look much like gastric glands As far as I know no one has ever published photographs showing oxyntic cells in these mythical isles The position then appears to be that adenocarcinoma may arise extremely rarely in the oesophageal glands

Cancer of the oesophagus may be papilliferous ulcerative or scirrhous It sooner or later causes obstruction but usually not until two-thirds of the circumference is involved By this time the growth has penetrated the thickness of the muscle coat Soon afterwards it will invade by continuity neighbouring structures such as pleura aorta bronchus lungs or diaphragm

The lymphatic drainage is in the main longitudinal as is the arterial supply The spread is in the first place along the important longitudinal submucosal lymphatics Bronchial aortic and other mediastinal nodes may be involved as well as left gastric or lower cervical Much emphasis has been placed on the well known fact that not only growths of the distal third but also of the middle third often give rise to a malignant gland at the origin of the left gastric artery whence the growth may spread to the pancreatic and coeliac glands It is to deal with such a wide spread that the "extended radical" operation for cancers of the lower third has been practised So much importance has rightly been placed on this distal spread that the cephalad spread has been somewhat neglected Many cases recurring after oesophagectomy have had glands all along the superior mediastinum and even in the neck a feature hardly ever seen before the advent of oesophagectomy There has been a tendency to "save" oesophagus above the growth—probably 3 centimetres should be the minimum point of section above the edge of the neoplasm The second fact is often evident in the case of adenocarcinomas of the cardia which may spread upwards along the aorta to glands as far as the hilum of the lungs Time and again surgeons have found malignant spread in the submucosal lymphatics on subsequent microscopical examination of the proximal cut edge of the operation specimen—even though the division appeared to leave a reasonable margin above the gross upper limit of the growth

How malignant is cancer of the oesophagus?—In general it may be stated that the malignancy of a cancer in any part of the body varies inversely with the depth of resectable tissue which surrounds it at the stage when its symptoms lead to its diagnosis The liability to recur after apparently adequate resection is another compact criterion In cancer of the oesophagus the Broders classification of the histology is of secondary importance The dominating factor is the surrounding anatomy of the oesophagus Once the growth gets outside the oesophagus it is going to invade vital structures like the lungs bronchi or aorta Moreover the lymphatic spread is often much more advanced than suspected It is now considered that cancer of the oesophagus is one of the more malignant growths in the body

DIAGNOSIS

There is only one constant symptom of cancer of the oesophagus—dysphagia Lesser symptoms however may occur early such as burning pain—interscapular or ensiform hiccups—in carcinoma of cardia and a cough Very occasionally

knowledge of these symptoms leads to an early diagnosis The site where the patient feels the food sticking is important If he states the food sticks at the ensiform then the cancer is at the cardia In a cancer anywhere higher up in the thorax the patient will say the food sticks at the jugular notch

The finger tips are worth looking at—they may show clubbing or koilonychia or sclerodactyly—giving a clue to some causes of dysphagia

Two investigations are essential in all cases of unexplained dysphagia an opaque swallow and oesophagoscopy in that order If carcinoma of the oesophagus is suspected it can only be excluded if both are negative

Radiological examination is notoriously unreliable in the cervical oesophagus and even in the thoracic region it may be misleading In growths in the ulcerative stage the appearance may be entirely missed if there is as yet no obstruction Moreover where obstruction is obvious the result needs confirmation for example a typical cardiospasm may be found to be a carcinoma and contrariwise an irregular appearance like cancer may be due to impacted food debris above a simple stricture

The surgeon should be *his own oesophagoscopist only in this way can he build* up his criteria of operability and compare his endoscopic findings with those on thoracotomy In the last few years some of the leading American surgeons have realized the importance of this integration The degree of fixity of the growth may show obvious inoperability The only anatomical variety likely to give rise to difficulty of diagnosis on oesophagoscopy is scirrhous It may look like a simple stricture of peptic or other origin Biopsy confirmation should always be made Whenever it is negative or non committal the whole diagnosis should be reconsidered before operation Bronchoscopy also should be done in growths of the mid oesophagus It may indicate inoperability from bronchial invasion or carinal widening from malignant mediastinal glands

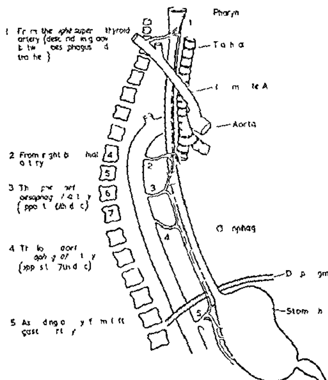
THE BLOOD SUPPLY OF THE OESOPHAGUS

At one time the poor blood supply of the oesophagus was prominently men tioned among the difficulties of the surgeon and anastomotic leakages were thought to be often due to this cause In the course of operations for cancer of the middle third where the growth has proved inoperable the author has on several occasions mobilized the oesophagus up to the growth at the level of the bifurcation of the trachea in order to allow the fundus of the mobilized stomach to be anastomosed to the oesophagus above the *vena azygos major* This by pass operation gives adequate palliation and in no case has the distal half of the thoracic oesophagus shown any sign of lack of blood supply It is to be noted that in these cases there is no blood supply except that reaching the oesophagus at the level of the aortic arch the right bronchial artery and the gastro epiploic and pyloric branches supplying it *via* the stomach

The arteries of the oesophagus

In spite of the vast industry of oesophageal surgeons in the last few years the description of the arterial supply in anatomical books and even in surgical mono graphs is distinctly cavalier It usually runs somewhat as follows The arteries

PLATE II



The arteries of the oesophagus in man

supplying the oesophagus are the inferior thyroids branches from the inter costals and the aorta the inferior phrenic and the left gastric Shapiro and Robillard (1950) have contributed a useful description of the arterial supply based on 50 dissections

There are five constant arteries supplying the oesophagus the inferior thyroid (right chiefly) the right bronchial artery the upper thoracic oesophageal the lower thoracic oesophageal and the left gastric In a fair number of cases there are accessory branches from the subclavian (right and left) the thyroidea ima left bronchial artery a third aortic oesophageal and inferior phrenic The inferior thyroid gives a longitudinal branch which runs in the tracheo-oesophageal groove supplying both oesophagus and trachea and anastomosing distally with the bronchial branch There is in fact a substantial longitudinal or vertical artery running between most of the fine segmental supply trunks The right bronchial artery comes from the third or fourth intercostal artery or direct from the aorta In 90 per cent of all cases *only two* aortic branches are found between the bronchial artery and the diaphragm These are the aortic oesophageal arteries—they are almost always unpaired and arise to the right of the mid line—the upper at the level of the sixth intevertebral disc and the lower at the seventh disc The latter is larger and longer—maybe 2–3 inches long Both of them course to the posterior aspect of the oesophagus bifurcating into ascending and descending divisions which inosculate with the arteries above and below The left gastric oesophageal branch is constant and important It runs up behind the oesophagus and anastomoses with the inferior aortic oesophageal—very seldom with the inferior phrenic

The following observations have to be made Extensive freeing of the cervical oesophagus from the trachea is liable to cause sloughing as the vertical collateral in the tracheo-oesophageal groove is easily damaged and the downward flow from the superior thyroid is small Similarly stripping of the supra aortic oeso phagus impairs the blood supply in the many cases where there is no demon strable vertical artery between the inferior thyroid and the bronchial This fact is specially important to surgeons who perform the left route operation for growths of the middle third The lower half of the thoracic oesophagus on the other hand may be freely mobilized

These points have been well illustrated experimentally by Swenson and others (1950) These experimenters used dogs and their conclusions were that the whole cervical oesophagus may be mobilized without sloughing Similarly the thoracic oesophagus from aortic arch to stomach If however the cervical and thoracic oesophagus is mobilized then sloughing occurs near the middle of the length in over half the cases While the arterial supply in another animal is no reliable guide to that of the human these experiments of Swenson and others give an academic imprimatur to the clinician s findings and serve to correct the erroneous beliefs of recent years about the blood supply

PRE OPERATIVE PREPARATION

Many of the patients with cancer of the oesophagus are dehydrated starved and septic and will require 2–3 weeks treatment in hospital before operation During this time the patient is assessed which one gathers means ordinary careful examination together with any investigations that may be indicated

The pre operative preparation may be usefully considered under three headings local nutrition and infection

Locally an oesophagoscopy will often show bad obstruction and stagnation The stricture should be dilated if the patient cannot swallow say minced meat The oesophagus above is thoroughly cleaned This may need repeating especially as the dysphagia may be temporarily increased by the first dilatation Care is taken not to give any food which will not pass the stricture

The patient s nutrition is improved by dilating the stricture and giving good quantities of high calorie liquid and semi solid food The dehydration usually masks the true state of affairs for example the haemoglobin per cent and the plasma protein it is important to repeat such estimations before the operation Carbohydrates and especially protein are required Milk raw eggs and finely minced meat in weighed quantities should be given—3 000 calories and 120 grams protein a day must be aimed at

Pre operative blood transfusion and plasma transfusion have some place—but the proteins the patient himself builds up from his food are what he really requires to withstand a major operation The vitamins must not be forgotten and in addition to fruit juices tablets of vitamin C and B may be ordered Hydrolysed casein has been little used and has on the whole proved more trouble than it is worth The key to pre operative building up of the nutrition is for the patient to elaborate his own proteins from those digested in his own intestine The question of jejunostomy to help the feeding is still not settled In itself it is a very valuable and certain method in patients who have almost complete obstruction It is wrong in these starved patients to refuse this simple and safe method of feeding just because it may get in the way of later exploration Both Clagett of the Mayo Clinic and Santy of Lyons employ the operation where necessary and they are undoubtedly right It can be done quite simply through a small grid iron incision well to the right of the mid line so that it is out of the way of later procedures Jejunostomy also solves the vexed question of early post operative feeding

Infection in general should be cleared up or abated Septic teeth must have sensible treatment—preferably not wholesale extractions as that would leave the mouth more septic than ever for 2–3 weeks Pre operative penicillin may be given for at least 2 days before—longer if there is purulent bronchitis or other gross sepsis The patient should give up smoking completely for 3 days before operation No other single factor will do as much to prevent post operative chest complications Some of the American surgeons have advocated a course of pre operative quinidine or digitalis as a preventive of post operative cardiac arrhythmias—but this seems dubious to say the least in persons with sound and regular hearts

CONTRA INDICATIONS TO OPERATION

As with growths elsewhere these are local and general The local evidence of inoperability may include fixity of the oesophagus extension to bronchus widening of the carina Further afield there may be malignant glands in the neck or mediastinum as shown by radiological examination metastases in the liver pelvic peritoneum or even bones

Of the general contra indications perhaps the commonest is a poor condition of the patient due to age or infirmity Chronic bronchitis and emphysema are also

common and it is wrong to attempt the operation in anyone with a really low exercise tolerance for example getting breathless walking in the ward or up one flight of stairs Here it may be well to mention the common occurrence in cases of oesophageal obstruction of a spill-over purulent bronchitis leading to bronchiectasis

Serious heart disease especially due to hypertension or coronary disease will be found a common bar to radical surgery In the main such cases will reveal themselves on ordinary activity in the house or in the ward

The urinary system in these patients—mostly male and over 60 years of age—must never miss scrutiny as impending prostatic retention and chronic renal failure may well turn the scales against the patient

SURGICAL TREATMENT

Growths of the lower end

Included under this heading are adenocarcinomas arising in or involving the cardia and squamous carcinomas arising near the cardia They may be roughly described as growths not extending above the lower fourth of the thoracic oesophagus inasmuch as there must be a wide margin of apparently healthy gullet removed above the growth and yet leave room for an anastomosis to be made below the arch of the aorta With the patient lying on the right side the eighth rib is resected and the chest opened through its bed This incision is carried in the same direction across the epigastrium practically to the mid line a little above the umbilicus the thoracic and abdominal cavities are freely opened If on examination the growth is found operable the diaphragm is divided from the hiatus to the periphery The mediastinal pleura is opened and if necessary resected

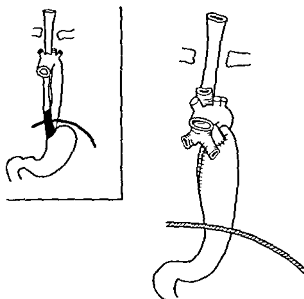


FIG 62.—Cancer of the lower end Schema of the Adams and Phemister operation (*By courtesy of G T Pack and C V Mosby Co*)

and a tape passed round the oesophagus which is mobilized The upper end of the stomach is then freed by dividing the gastro hepatic and gastro splenic omenta The left gastric vessels are divided at their origin and the upper part of the stomach completely freed In many cases removal of the spleen will make the operation easier A tape is now passed round the stomach and the part of the oesophagus bearing the growth is finally dissected as widely as possible together with any adherent diaphragm The upper third or so of the stomach and the oesophagus are then held upwards and above the wound and the stomach is brought up and fixed in the mediastinal gutter left by the oesophagus and held in place by several interrupted sutures between it and the mediastinal pleura The posterior sero muscular layer of the anastomosis is carried out before the removal of the oesophagus The oesophagus is then divided and its cut end is implanted into a small incision on the anterior wall of the stomach just below the top It is a good plan to remove a little circle of stomach care being taken not to make it too large If clamps are used either on the oesophagus or on the stomach they should be carefully protected with rubber sleeves They are best avoided relying on picking up the vessels and on suction to keep the field clean The next layer of the anastomosis is then carried out using fine interrupted silk with fine non cutting needles the knots being placed on the inside This is continued on to the anterior half of the through and through layer Finally the anterior serous layer is put in

The following points are most important (a) resection *en bloc* with an ample margin (b) absence of all tension on the suture line (c) a precisely sutured anastomosis with interrupted silk sutures and (d) the *mucosa* is the surgeon s sheet anchor in oesophageal surgery and must be snugly secured with each suture

Should the stomach in some cases be found rather short from having to resect part of it the upper part of the line of resection may be left open and joined directly end to end to the oesophagus as is done in a Billroth I operation This plan is followed by Norman Tanner and it is a very valuable alternative

A catheter draining through a stab wound and waterseal drainage are employed preferably for 7–10 days There seems no advantage in taking the catheter out in 48 hours as some surgeons advocate The catheter however may be disconnected and spigoted in a few days to allow the patient to get up

The diaphragm is then sutured leaving just enough room for the stomach without compressing it It is as well for 2–3 sutures to be placed through the stomach serosa and the diaphragm The chest wall and abdominal wall are now closed in layers

This operation is the Adams and Phemister operation of 1938 except that they used the purely thoracic approach There is no doubt however that the abdomino thoracic approach gives a superb exposure of this region of the body allowing freer and easier resection Garlock was the first advocate of the operation in recent years He turned the incision however into a vertical one at the outer border of the rectus but keeping the incision straight in its whole length is simpler and better (Tanner 1947)

The middle two-fourths

Torek s (1913) own classical case was a carcinoma at the level of the bifurcation of the trachea and he carried out his operation in spite of the anatomical difficulties through the left pleura He did not open the abdomen but closed

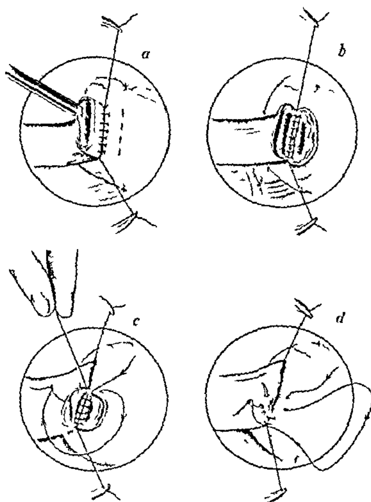


FIG 63 —Oesophagogastrostomy D tails of the technique
(*By courtesy of British Journal of Surgery*)

and inverted the lower end of the oesophagus The rest of the oesophagus with its growth was then pushed up into the neck and out on to the front of the chest where it was resected The patient was left with two stomas the cervical oesophagostomy and the gastrostomy They were joined by a rubber tube for swallowing Such rubber tubes are difficult and unreliable and many methods have been used of constructing an artificial antethoracic oesophagus The most reliable of these methods is undoubtedly the jejunal one where a length of jejunum is brought up beneath the skin to be anastomosed with the oesophagus Such operations are difficult and give rise to repeated disappointments however and very few cases of resection for carcinoma have lived long enough to have a successful artificial oesophagus completed It then became obvious that some method should be attempted of applying the principles of the Adams and Phemister operation

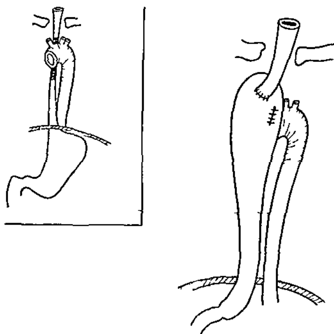


FIG 64 Cancer of the middle two fourths Schema of the Ivor Lewis operation—R transpleural resection with oesophagogastrostomy (*By courtesy of G T Pack and C V Mosby Co*)

to growths of the mid oesophagus Garlock (1944) reported the method of transposing the upper stump after doing a resection on to the outer side of the aortic arch and bringing up the stomach as in the lower end case and making the anastomosis at the level of the arch This method had the drawbacks inherent in the left pleural approach for cancers of the mid thoracic oesophagus as well as the uncertainty of the blood supply to the considerably mobilized upper stump The second method is the right transpleural method first used by the author in 1944 This involves *two incisions first abdominal then right thoracic* The advantages of the right transpleural approach for growths of the middle two fourths are (a) far better accessibility to the oesophagus as only the vena azygos major has to be divided to lay bare its whole course and (b) the aortic arch instead of being an obstacle becomes a safety barrier between the surgeon and the other

pleural cavity Moreover he can do the whole resection in full vision instead of working bluntly and blindly By freely mobilizing the stomach beforehand right up into the hiatus there is no difficulty in drawing it up into the thorax and in all patients who are in reasonable condition the two stages of the operation are finished the same day However the method has the great advantage that in patients in poor condition the actual resection can be postponed for a week or so The side chosen for the operation of oesophagectomy should be that giving the better exposure of the site of the growth Therefore to operate on the mid oesophagus through the left pleura is as unanatomical as it would be to operate on the lower end through the *right* pleura

Description of operation for the middle two-fourths

Stage I—An upper left paramedian laparotomy is done The abdomen is carefully explored If there are no metastases the greater curvature of the stomach is freed in its upper half The vasa brevia left gastro epiploic artery and the omentum are divided well away from the stomach leaving the vascular arch attached to the greater curve The gastro hepatic omentum is then divided again well away from the lesser curve and the left gastric artery is tied near its origin To reduce inflammatory reaction and adhesions fine silk should be used throughout and the most careful haemostasis secured The abdominal wall is now closed and the patient turned on his left side and re draped for Stage II

Stage II—With the patient in the left lateral position and a sandbag under the chest the whole of the right sixth rib from the neck to its cartilage is removed and the chest entered through its bed If after careful examination the growth seems removable the lung is packed forward and the vena azygos major divided between ligatures The mediastinal pleura is then incised and just above and below the growth pieces of tape are passed round the gullet to be used as guy ropes The involved segment together with any glands is then slowly dissected free Care must be taken to avoid opening the left pleura—a troublesome complication There is no need to paralyse the phrenic nerve The lower end of the oesophagus is gradually freed by retracting the diaphragm dividing the branches of the vagi and keeping it on the stretch with spongeholders The part in the oesophageal hiatus is then freed with the index finger A specially devised sickle shaped retractor is now insinuated into the hiatus This instrument not only retracts with its tapering end but holds the diaphragm and underlying liver out of the way As soon as the cardia is drawn up through the hiatus the peritoneum is severed all round the circumference By steadily drawing on the cardia the fundus and eventually the body of the stomach are brought up into the pleura Adhesions of varying strength will have formed if there was an interval since the first operation—they are separated When the stomach is sufficiently mobilized so that the fundus reaches well above the growth the oesophagus with a wedge of cardia is severed and the gap sutured and invaginated (if any enlarged glands have now become evident along the upper part of the lesser omentum it is safe to extend the excision to include part of the lesser curvature and still leave the fundus viable the vascularity of the stomach is remarkable) The next step of the operation is to prepare a gastric bed on which the oesophagus will lie The upper end of the stomach is fixed in the angle between the vertebral bodies and mediastinum Five or six

interrupted silk sutures are placed along each edge—posteriorly fixing the stomach to the anterior spinal ligaments and anteriorly to the anterior cut edge of mediastinal pleura The oesophagus is then laid upon the stomach and the posterior layer of interrupted sutures is put in before cutting off the growth A transverse incision is made in the stomach or a small disc may be cut out The actual anastomosis is then carried out as for the lower end operation Finally if it can be done easily the stomach edges or omental fringes are folded over in front of the anastomosis and lightly sutured The enlarged hiatus does not need stitching up it is only about the circumference of three fingers 3–4 sutures are however placed between the stomach and its rim to prevent small gut passing through So well does the stomach fit the hole however that this is probably not necessary 200 000 units of powdered penicillin are sprinkled around the anastomosis A No 14 catheter is placed alongside the anastomosis with a second hole cut lower down to lie just inside the pleura This is brought out through the ninth inter costal space laterally to drain under water

The chest wall is sutured in layers

During the stitching up the anaesthetist endeavours to get the lung well ex panded Any air left is drawn out forthwith by suction to the catheter Blood transfusion is given throughout the operation If there is any appreciable amount of bronchial secretion a careful bronchoscopic cleansing is done before the patient leaves the table

Right or left approach to the mid oesophagus?

In the United States of America the great experience and consequently great influence of two men—Garlock and Sweet—for several years was decisive in favour of the left pleural approach In Great Britain and in France (Santy) the right approach has been largely used Resano of Buenos Aires at his remarkable clinic for oesophageal surgery has favoured this method At the 1949 annual meeting of the American Association of Thoracic Surgery however the right sided approach was a principal subject for discussion Kent (1950) and Harbison Macmanus (1950) and Paine were strongly in favour of the operation and both Poole and Chamberlain pointed out how simple it is to do a palliative by pass operation where the growth is found not resectable Several surgeons also con firmed the great advantage in the right operation of leaving an uncut and fully acting diaphragm Sweet (1950) now admits that the operation through the left pleura is more difficult and that the mortality of his mid thoracic operation is twice that of the lower end His main objection to the right sided operation however remains that at the second stage on opening the thorax the case may be found inoperable and so the abdominal operation will have been done for no purpose Anyhow Sweet challenges if anybody else can show a lower mor tality or longer survival than he has then he may change his method The answers to these two points are quite simple In the 35 per cent of cases where the growth is found not resectable the stomach and lower oesophagus are just brought up and a by pass oesophagogastrostomy carried out As for the other point Sweet is justly proud of his low mortality but this is nearly twice as high in the mid oesophagus as the lower oesophagus therefore the reasonable test would be for him to carry out a series of right sided operations himself and then compare

Opinions varied on the value of jejunostomy and on the wisdom of waiting between the stages The question of jejunostomy has nothing to do with the right or left controversy As for the interval between the stages most surgeons advocate that the two stages be done forthwith on the same day unless the patient is in too poor a condition but when an interval is necessary the method provides the ideal staging and the re adherence of the stomach will be negligible if the resection is done within seven days The modification of Macmanus dividing the right crus of the diaphragm seems unnecessary as the pyloric antrum just fits the dilated hiatus normally produced The ease with which a by pass operation can be carried out by this method in inoperable cases answers the only substantial objection namely that the first stage may have been carried out for nothing As was admitted in the discussion the method gives a better approach to the oesophagus and better resectability from the point of view of cancer surgery It was pointed out how much easier it is to remove an adequate amount of proximal oesophagus how much shorter the thoracic cavity is open and how much easier it is for the right handed surgeon to do an anastomosis high in the chest on the right than on the left—no small point

POST OPERATIVE MANAGEMENT

Before the patient leaves the table it is a good thing to do a bronchoscopic cleansing as a routine

For the first 24 hours continuous oxygen is a great help and the simplest and best way of giving it is through two nasal catheters Oxygen tents are oppressive for the patient and discourage frequent nursing attention and the B L B mask although excellent in a normal person is seldom kept properly applied in a very ill patient

Intravenous drip should be maintained until the circulation is satisfactory

The staff should avoid propping the patient up too soon Many cases of collapse are due to this being carried out abruptly

The keeping of the respiratory passage clear of secretion is the other main consideration The patient is unable to cough for 48 hours post operatively unless the chest is firmly held by an attendant The nurse should be taught the paramount importance of regular coughing in these patients and learn how to hold the patient If the bronchi are still moist with secretion in spite of efforts to clear them then bronchoscopy must be done without further waiting and repeated if necessary A skiagram of the chest is taken daily for three days and on three alternate days thereafter

Post-operative feeding

In cases who have a jejunostomy this is no problem In the others however (this will be the majority) intravenous fluids will have to be maintained for 2–3 days Nothing should be given by the mouth except ice or an occasional sweet to suck About the third day one ounce of barium swallow is given and if its passage is clear and uninterrupted down into the duodenum feeding may be commenced as for a gastrectomy that is to say one ounce feeds every hour to begin with On the fifth day a radiological check of the swallowing can be done again

An alternative method of post operative feeding is to leave an indwelling Ryle s tube just past the anastomosis and employ continuous gravity suction The patient may then have fluids from the start There is no evidence to support the mis givings that several surgeons have expressed about an indwelling tube in these cases With a satisfactory tube the patient can be given small drinks from the start with much advantage to his morale

By the eighth day he should be able to take semi solid food up to three ounces at a time and by the fourteenth day should be able to take solids

Occasionally there is trouble from regurgitation this can be avoided by always sleeping propped up

The patients may be got out of bed within 4–5 days earlier if they feel like it and after about three weeks they can be discharged

Post operative complications

Shock —Post operative shock in an operation lasting from 3–5 hours is often likely to be severe It is remarkable however how it can be avoided in most of the younger patients by timely treatment during the operation The first line of defence is the skill of the anaesthetist inasmuch as respiratory embarrassment leads more surely than anything else to cardiovascular collapse The second line of prevention is prudent and adequate blood transfusion the speed of which is varied according to the loss With successful attention under these two headings it is remarkable in what good condition these patients can leave the table

The treatment of shock after return to the ward is to continue the same two principles namely to maintain adequate oxygenation and continue transfusion when necessary Plasma should be substituted for blood after the point of re placement of lost blood has been reached It is of course vital not to allow the patient to remain near the stage of irreversible circulatory collapse for a moment longer than can be avoided so that resuscitation must be energetic and early Patients must not be propped up until they are of good colour and have a good pulse

Without giving a comprehensive list apart from shock the main post operative complications may be grouped under three headings infection of the operative field cardiac complications and pulmonary complications

Infection of the operative field —This is due to contamination or leakage It may take the clinical form of an empyema mediastinitis or suppuration with breaking down of the wound The prevalence of serious infection apart from leakage was never high with present day technique and has become negligible since the use of antibiotics Similarly leakage has become steadily rarer with the greater care in carrying out the anastomosis Nevertheless early leakage within the first week usually ends fatally Later leakage however may well result in an empyema which the patient gets over As in other major thoracotomies serious infection of the wound itself is unusual and even if a pyopneumothorax develops the wound will fortunately have become sealed off in time Most surgeons make a practice of giving prophylactic penicillin post operatively by the systemic route as well as the instillation of penicillin locally into the chest at the end of the operation

Cardiac complications —Post operative death from coronary thrombosis is occasionally seen and proved *post mortem* It is not so common however as

alleged in some large statistics The term has probably been used to describe cases which really died from shock or infection There are two interesting cardiac arrhythmias which occur in about a quarter of the cases of oesophagectomy and commoner still in the high resections These are auricular flutter occasionally and auricular fibrillation frequently The sudden disorder of rhythm is alarming to the patient and his attendants and undoubtedly militates to some extent against his recovery The onset is usually some days after the operation and even cardiologists now recognize the relationship of these cases to pneumonectomy and oesophagectomy

Treatment—The best thing with the coronary case is to try and weed out the likely patients beforehand and reject the ones with evidence of coronary insufficiency As for the arrhythmias American surgeons have been giving preoperative digitalis prophylactically I have no experience of this Should fibrillation occur however digitalis or Digoxin is given under the physician s care until the irregularity ceases usually a matter of a few days This disordered action seems to occur quite irrespective of any cardiac disease Nevertheless it is as well to get it under control by digitalis or quinidine

Pulmonary complications—These are purulent tracheobronchitis atelectasis bronchopneumonia and spontaneous pneumothorax Purulent tracheobronchitis is the commonest of the serious complications of oesophagectomy Its prophylaxis is largely in the hands of the anaesthetist Recently attempts have been made to avoid tracheal catheters during anaesthesia relying instead on packing the oesophagus This practice shows considerable promise At the end of the operation if the respiratory tract is moist careful bronchoscopy should be done and all pus and mucus cleaned away For the first three days after the operation it is extremely difficult for the patient to cough effectively because of the pain in the chest wall All the nursing staff should be instructed in effective holding of the patient s chest while he coughs This greatly reduces the pain Nevertheless in about half the cases in Great Britain one finds it necessary to carry out one or more bronchoscopies to clear the bronchi The time to do a bronchoscopy for this condition is when the surgeon first asks himself the question I wonder whether we ought to do a bronchoscopy? If this query comes to the mind the answer always is yes and the time is straight away To leave the case overnight saying If he is not better in the morning is practically always a mistake The accumulation of mucopus may be so great that bronchoscopy may have to b repeated 2-3 times in 24 hours with an eventual successful result Indeed unless the patient is cold and nearly pulseless one should not despair of ultimate success in this very difficult complication

Atelectasis—Atelectasis is really a complication of the purulent bronchitis and is similarly treated by bronchoscopy Bronchoscopy may have to be repeated until the patient is able adequately to cough

In connection with these two complications it is to be observed that both of them can be dealt with by efficient coughing If the wound could be made painless then coughing could be effective Various methods have been tried to make the wound painless such as crushing the intercostal nerves above and below the use of slow acting local anaesthetics and latterly intravenous nupercaine

Bronchopneumonia—This may be due to aspiration of oesophageal contents or

merely to accumulation of mucopus Treatment is on general lines all these pulmonary complications needing continuous oxygen preferably by the simple and adequate method of two nasal catheters Little is nowadays heard about the sulphonamides in this condition Aureomycin will sometimes bring about a dramatic abatement of the infection

Spontaneous pneumothorax — This is an occasional complication which may be due to the operation or more frequently due to coincidental rupture of a bulla These cases are best treated by applying continuous suction to the tube and the administration of oxygen

In all these pulmonary complications it will be seen that there are three major considerations first the keeping of the respiratory tract clear of debris mucus and pus secondly the encouragement of effective coughing and thirdly the adminis tration of continuous oxygen if there is any respiratory embarrassment or cyanosis

Two or three other complications merit mention Uraemia in these elderly patients is not uncommon and a distended bladder should always be looked for even if the symptoms do not suggest it If there is a history of frequency by night the renal function should have been checked pre operatively Chylothorax injury to the thoracic duct in middle and upper oesophagectomies is a real hazard It is a matter of little importance however if recognized at the time and the two ends of the duct tied If it is not recognized it will usually result in the patient s death as a second thoracotomy within a few days for the purpose of finding and tying the duct even if successful is likely to be too much for the patient

Leakage —Early leakage is going to be serious and almost certainly fatal In late leakage however when the lung is well expanded and is stuck to the parietes it is well worth while persevering in the hope of saving the case The most rational procedure is probably to keep a moderately large tube in the chest draining under water but not to apply suction to it A Ryle s tube should be swallowed as far as the anastomosis and continuous suction applied to that That is applying the principles known to be successful in perforations of the stomach when the patient cannot stand a major operation

Diaphragmatic hernia —This with intestinal obstruction has accounted for an occasional death

Haemorrhage —Haemorrhage from a large vessel such as the aorta may be due to a localized leakage at the anastomosis with a suture encroaching on the aortic wall or to a peptic ulcer at the anastomosis eroding the vessel wall

Stricture of the anastomosis —This may occur after oesophagogastrostomy in spite of the use of interrupted sutures The reason as emphasized by Barrett (1949) and by Allison and Borrie (1949) is the liability of the oesophageal mucosa to digestion This complication is fortunately not prohibitive in operations for carcinoma largely due to the vagotomy entailed A fair number of the longer survivors need occasional dilatation however

ON PALLIATIVE TREATMENT

The worst disability of the patient with inoperable cancer of the oesophagus is that he cannot swallow and any procedure for palliation will be judged by the patient in this light A gastrostomy for example whatever it may do in prolonging

a little the patient's life does not enable him to swallow again Most surgeons therefore have come to agree with patients that gastrostomy is a poor operation for someone who will die of carcinoma in a few months

Souttar's tube

There has been a decided return to favour of Souttar's tube where the growth is obviously inoperable and no exploration even is indicated The stricture is first carefully dilated and the tube threaded over a bougie which has been introduced through the lumen This simple measure gives substantial relief to the patient The danger of the method is perforation of the oesophagus—not common in experienced hands The tube may be vomited or passed in which case try again with a better fit The commonest trouble is blocking of the tube with food debris Allison's tip is excellent here the patient swallows any fizzy drink such as soda water Occasionally oesophagoscopy may be necessary—when husks or orange pips have been swallowed!

Sometimes when the tube falls out the channel has been so eroded by it that the patient will not need another for weeks

Palliative resection with oesophagogastrostomy

As has been said already the majority of the oesophagectomies with anastomosis done in the last 10 years have really been purely palliative operations from the start But the palliation often lasts a year sometimes 2 years and recurrence seldom causes a return of the obstruction It is a fact that in most cases removal of the growth makes a palliative oesophagogastrostomy much easier whatever the result

By pass operations

Where the growth is firmly and extensively fixed and an exploration has been carried out the obvious treatment is a *by pass anastomosis of the oesophagus* above the growth to the fundus of the stomach This is very simple in growths of the cardia after dividing the diaphragm the gastro-splenic ligament and left gastric artery a side to-side anastomosis is made It has been mentioned that in the Lewis operation for cancer of the mid-oesophagus a similar operation is carried out when it is found that the growth is irremovable In this way the patient will have had the best possible palliation and not face the sorry fact that nothing could be done in spite of all he has gone through

An alternative by pass operation is to use a jejunal loop or better a jejunal length *a la* Roux to anastomose with the oesophagus above the growth This is chiefly called for where the stomach is considerably involved and it is considered that a Souttar's tube is unsuited for the case

Radiotherapy —Radiotherapy is of great palliative value in some cases chiefly cervical and supra aortic (*see* below)

The upper oesophagus

Cervical oesophagus

These growths are mostly post-cricoid and commoner in women Mikulicz as long ago as 1886 reported a case where he had performed a resection and restored

continuity by means of a skin tube This method was revived 30 years later by Trotter (1932) and 50 years later by Wookey (1940) but on the whole surgeons feel that radiotherapy is *the treatment of choice* as a good percentage of the cases respond well and remain free of symptoms for as long as they would with resection It must be admitted however that the best cases of radiotherapy are not as impressive as the few outstanding results of resection such as Arthur Evans case

Supra aortic oesophagus

There is a stretch of oesophagus in the thoracic inlet from about an inch above the manubrium to the angle of Ludwig which is difficult of approach both from the neck and the thorax This no man s land (Leading Article) is still more

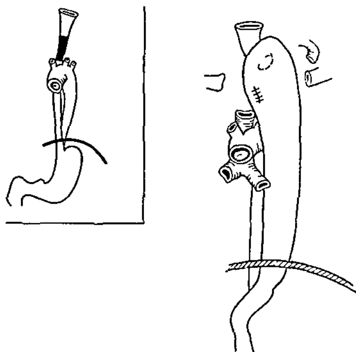


Fig 65—Supra aortic cancer of the oesophagus Schema of intracervical oesophagogastrostomy (*By courtesy of G T Pack and C V Mosby Co*)

a problem in regard to restoring the alimentary continuity after resection It lies opposite the upper four dorsal vertebrae In 1948 however both Garlock and Sweet reported cases where they had resected the growth together with the whole thoracic oesophagus and then brought up the gastric fundus through the left thorax up into the neck and completed the operation as a cervical oesophagogastrostomy A number of other cases have been reported since both for carcinoma and simple stricture The thoracic inlet is packed tight with important structures and a good deal more room is obtained if the inner third of the clavicle and the anterior half of the first rib are resected The thoracic duct and recurrent nerves and the vagus trunks are in danger

The growth is first explored from the neck using an incision along the anterior border of the left sternomastoid The oesophagus is freed down into the thorax

and if the growth seems operable then the left thorax is opened If the growth still appears operable the whole thoracic oesophagus is mobilized the diaphragm opened widely and the stomach completely mobilized as in the mid-oesophagus operation There are two technical differences however the oesophagus is divided at its lower end and its stump invaginated into the stomach that is all the lesser curve must be preserved and secondly the left gastric branches are divided close to the gastric wall so as to allow full stretching of the stomach The fundus can now be brought up into the neck The chest is closed and the neck wound is re opened the oesophagus delivered and resected The fundus of the stomach is sutured to the prevertebral fascia and an end to side anastomosis carried out just below the cricopharyngeus

It is important to spare the cricopharyngeus to avoid damage to vagi and recurrent nerves and the thoracic duct The gastric vessels need very judicious handling so as to get the maximum reach of stomach while preserving an adequate blood supply

Post-operative pressure on the anastomosis from oedema and too little room is to be expected particularly if the bony cage has not been enlarged

Bricker and Burford have described another operation for some of these growths of the no man s land —using a pedicled skin tube for the subsequent bridging of the gap It is several months before the operation can be completed

These resections are undertakings of great magnitude some of the reported operation times varying from 6¼-9½ hours and none of the cases so far published has been very favourable from the point of view of cure Hence the practical conclusion must be that in supra aortic growths like post-cricoid external radiotherapy should be tried in the first place as the chance of satisfactory palliation is good (Lewis 1946)

In cases which do not respond then resection should be done if they appear operable if inoperable then dilatation followed by Souttar s tube Yudin s jejunal operation seems hardly a practical proposition for the same reason as after the Torek operation it is uncertain and takes too long An operation for the palliation of inoperable cancer should be simple and one stage

THE PLACE OF RADIOTHERAPY

In all cancers of the cervical oesophagus it is probably worth trying to see if they are radio sensitive If so then radiotherapy is the treatment of choice but even in this region no result has equalled the 30-year surgical cure of Arthur Evans There are however a number of over 10 years such as Abel s case and B om hall s case reported by Lewis This patient lived for 10½ years eventually dying of a recurrence involving almost the whole oesophagus

In the thoracic oesophagus the radiotherapist s difficulty is giving an adequate tumour-dose at the required depth without serious injury to the skin and viscera accuracy is also essential

Radium cavitary

Guisez has been the chief exponent of radium in the lumen for cancer of the oesophagus For 30 years he has used the method and has reported 4 cases alive and well at 15 years and 1 case a doctor whose growth recurred after 26 years

It is only where the growth can be dilated to allow a stomach tube to pass that Guisez s method can be used The radium tubes containing 20–80 milligrams are fixed in the lumen of the container at the required distance and placed in position for 5–6 hours daily for a fortnight or more

All that can be said is that others have not been able to emulate Guisez s results

Kurtzahn for example developed a very exact procedure using an endless sound through a gastrostomy the position of the tubes being checked at each sitting by a radiograph All his cases were relieved sometimes for a year or more

Lederman again put in much work on making the dosage throughout the length of the growth even by neutralizing the gaps between the adjacent tubes This he did by regular shifting of the tubes However out of 33 patients treated only one survived 6 months

It may fairly be said that Guisez alone has made any curative claims for the method Other careful workers have all been disappointed Indeed anything like an adequate depth dose would appear impossible and therefore only the earliest growths could possibly be affected As for the average growths surface necrosis may be expected to open up the lumen and so give some temporary palliation

Interstitial radium treatment

Radon seeds have been inserted through an oesophagoscope with occasional palliation Steele of Guildford reported his method of combined fore and aft oesophagoscopic implantation (through a gastrostomy) with one case alive and well three years afterwards

The insertion of radon seeds into the exposed oesophagus has also been tried by Howarth Cleminson Negus and others It is almost impossible to secure even and adequate distribution by any of these methods though occasional gratifying palliation has been reported

External radiation

It should now be recognized that primary healing and an occasional cure can be obtained by external radiation The radium bomb has been used in some of the cervical cases but mostly x ray therapy entirely so in the thoracic cases By using 4–6 ports—half from the front and half from the back—it is possible to deliver something like an adequate tumour dose to the growth while sparing the other organs as much as possible Levitt of St Bartholomew s Hospital London reported a good palliative result in over 60 per cent chiefly in the upper third however He admitted that growths of the middle and lower thirds only do well for perhaps a year or two but so far no patient has survived longer than 2½ years Levitt notes the cough and dyspnoea produced in these cases however

A most interesting recent attempt to counter the evil effect on other organs while at the same time delivering something like an adequate tumour dose is that of rotation therapy Nielsen and Jensen of Copenhagen have developed the method The patient is rotated through a complete circle during each treatment the beam being continuously checked by fluoroscopic control and some barium in the oesophagus The patient at the end of the treatment has a narrow band

of tanning round his chest In this way they are able to achieve a tumour dose of some 5 000 r with the least possible skin or general reaction 15 per cent live over 2 years

Zuppinger of Zurich dismisses combined cavitary and external radiation as being unnecessary and undesirable If the external radiation is adequate then the cavitary is not required and it increases complications

In conclusion it may be said that it is now just possible by the method of external radiation to deliver a lethal tumour dose to a cancer of the oesophagus without too great damage to the viscera It is accepted that for squamous cancer elsewhere this dose should be 6 000 r at least With the narrow fields and difficult calculations however the dose received by the tumour may be subject to wide errors and a sensible check should be obtained by inspecting the response by oesophagoscopy say once a week during the course as advocated by Lee (1941)

RESULTS

The mortality of oesophagectomy has fallen from the region of 100 per cent to about 30 per cent in the course of 20 years This is due about equally to advances in anaesthesia and in surgery A few surgeons have reported series below 20 per cent in cancer of the lower end The mortality varies greatly with the age and with the level Sweet in 166 cases reports the following death rates at various ages under 45 years—7 per cent 45–55—11 per cent 55–65—16 per cent over 65—22 per cent As for levels mid oesophagus 23 6 per cent lower end 13 per cent A fair approximate overall figure for oesophagectomy in good hands however is around 30 per cent

When we come to consider survival and cure the answer is more difficult In the first place it must again be pointed out that of all the hundreds of cancers of the oesophagus resected in the last 10 years at least 2 out of 3 were inoperable in any pathological sense and as Garlock has said one of the prime needs at present is for the surgeon to state clearly at the end of each case whether it was operable or not It is probable that the operable cases are really only the growths which have not extended through the oesophageal walls All the other resections are palliative

As for the late results it is heartening to learn that Adams and Phemister s first case operated on in 1938 is still alive and well having now outstripped Torek s famous case of 1913 The available recent figures of some of the surgeons who have done most cases are Resano s longest survival out of 155 cases is 6 years for the lower end and 5 years for the mid oesophagus Allison states that the prognosis is worse the higher the growth and this is the general experience Sweet out of 86 cases operated on over 3 years had 21 live 3 or more years = 24 per cent he had only 23 successful operations of over 5 years standing but of these 8 patients were alive and well

The following are Garlock s most recent figures (1951) He has one Torek s excision alive and well 14 years later

His operability rate for squamous carcinomas (irrespective of site) is 40 per cent and 40 out of 56 survived the operation He has 25 alive and well 9 of them over 5 years of which one is 11 years 2 of 10 years and 2 of 7 years

He has resected 74 out of his 142 cases of adenocarcinoma of the cardia (= operability of 52 per cent)

The overall mortality was 32 per cent and in the last 25 cases the operation mortality has been 10 per cent He has 9 alive over 5 years of whom 1 is of 10 2 of 9 2 of 8 and 2 of 7 years

Figures such as these suggest that in cases of cancer of the oesophagus really operable (rather than resectable) the prognosis may compare favourably with cancer of the stomach and certain other sites in the alimentary canal

REFERENCES

Adams W E and Phemister D B (1938) *J thorac Surg* 7 621
Allison P R and Borrie J (1949) *Brit J Surg* 37 1
Barrett N R and Franklin R H (1949) *Ibid* 37 194
Benciolini F (1930) *Arch ital Otol* 41 170
Bricker E M Burford T H and Eiseman B (1949) *J thorac Surg* 18 304
Carrie A (1950) *Brit J Surg* 37 474
Garlock J H (1938) *Surg Gynec Obstet* 66 534
— (1942) *Ibid* 74 555
— (1944) *Ibid* 78 23
— (1948) *Surgery* 24 1
— (1951) Personal communication
Kent E M (1950) *J thorac Surg* 19 559
Leading Article (1949) *Lancet* 2 1139
Lee S (1941) In Sir Stanford Cade s *Malignant Disease and its Treatment by Radium* 2nd ed Vol II Bristol Wright
Lewis I (1946) *Brit J Surg* 34 18
Macmanus J E (1948) *Surgery* 24 9
Phemister D B (1951) Personal communication
Resano J H (1950) *Prensa méd argent* 37 866
Shapiro A L and Robillard G L (1950) *Ann Surg* 131 171
Sweet R H (1944) *J thorac Surg* 13 4?3
— (1948) *Surgery* 24 929
— (1949) *Advances in Surgery* Vol II p 78 New York Interscience
— (1950) *Thoracic Surgery* St Louis Mosby
Swenson O and colleagues (1950) *J thorac Surg* 19 46?
Tanner N (1947) *Postgrad med J* 23 109
Torek F (1913) *J Amer Med Ass* 60 1533
Trotter W (1932) *Proc R Soc Med* 25 431
Wookey H (1940) *Brit J Surg* 27 696

CHAPTER 10

OESOPHAGEAL TRAUMA

N R BARRETT

DEFINITION

THERE are two groups of abnormalities namely traumatic perforations which permit extravasation cellulitis and suppurative mediastinitis and injuries due to swallowed corrosives burns and impacted foreign bodies These conditions will be considered separately although they frequently exist together

PERFORATION AND MEDIASTINITIS

Frequency —Wounds of the oesophagus are rare they were not mentioned in the British or American histories of World War I or in the review of chest injuries by Tudor Edwards (1943) They occurred but the associated lesions were generally so serious that the patients did not survive Apart from wounds there are circumstances such as endoscopy accidents of sword swallowing attempts at suicide by cutting the throat surgical operations and crush injuries of the thorax in which a perforation of the gullet can occur Neuhof and Jemerin (1943) analysed 40 cases secondary to instrumentation or to foreign body in the oesophagus in 19 perforation was due to passage of instruments (oesophagoscopy 10 gastroscopy 3 stomach tube 2 Plummer dilator 2 bougie 1 Levine tube 1) In 18 foreign bodies were the cause and in 3 there was a combination of both instruments and a foreign body The age incidence was from 9 months to 75 years

Until recent times the effects of perforations of the gullet could not be importantly influenced by treatment but prompt diagnosis and accurate surgery can save the majority of these patients

Modes of injury —The oesophagus may be torn longitudinally it may be ruptured in part or completely and the forces responsible for the injury may act from the outside or be a burst due to a sudden rise of pressure within the lumen Bullets and fragments of metal lodged adjacent to the intact gullet can penetrate slowly into the lumen by pressure necrosis or suppuration and the foreign body can then be passed per rectum

Pathology and anatomy

The oesophagus has a good blood supply and heals quickly provided the peri oesophageal tissues do not get infected Animal experiments and operations performed in man have shown that the absence of a serous outer covering does not delay or prevent healing of incisions tears or anastomoses The danger of a perforation is the cellulitis which develops in the surrounding tissues When a perforation has occurred liquid and gas escape through the hole and the inflam mation produced may be locally confined or spread In a few patients the march

of events is relatively slow the inflammation becomes circumscribed and an abscess forms this may resolve or more probably it may steadily increase in size showing little tendency to come to the surface and extending widely through the retrovisceral space In others there is little attempt at localization a fulminating cellulitis advances through the mediastinum and the patient dies as the result of toxaemia within a few days In yet others a tense collection of inflammatory fluids forms round the perforation and ruptures or leaks into the pleural cavity so that the patient develops a pleural effusion or a tension pneumothorax As the gullet is normally empty the first extravasated liquid is sterile mucus but soon

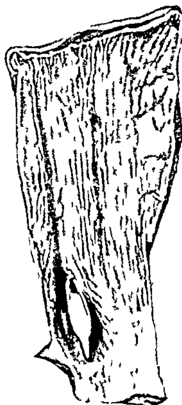
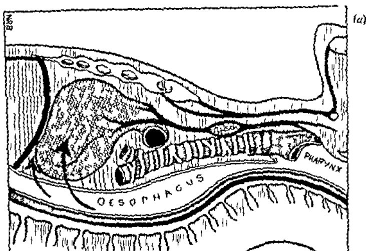


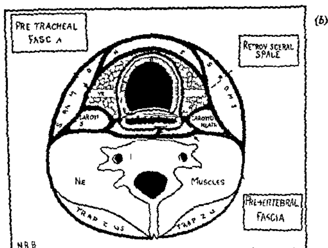
FIG 66—A *woman aged 40 was admitted to hospital* complaining of long standing achalasia of the cardia The obstruction was treated on many occasions with a mercurial bougie and ultimately by dilatation under anaesthesia At this last manoeuvre the surgeon must have caused the perforation depicted in this drawing for the patient complained of severe thoracic pain on coming round from the anaesthetic and died of suppurative mediastinitis 2 days later The drawing is of the outside of the gullet and shows no attempt at localization of the inflammation

other fluids such as saliva drink taken to relieve thirst and secretions regurgitated from the stomach also pass through the perforation The mediastinal effusion is an inflammatory exudate which contains bacteria gas food particles water (or other drink) enzymes and hydrochloric acid

The gas is air which has been swallowed Bubbles are sucked during each inspiration from the lumen of the gullet and travel far from the perforation in the areolar tissues of the mediastinum they may be palpated at the root of the neck or seen in radiographs above or below the diaphragm They spread so that within a few hours of a perforation in the posterior mediastinum *surgical emphysema* may sometimes be felt in the neck It is important to know that the bacterial inflammation lags behind the spreading edge of the surgical emphysema so that

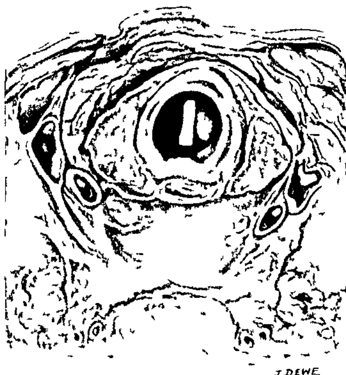


(*a*) This diagram is devised to show the position of the retrovisceral space which has been coloured red relative to the oesophagus In the neck infections in this space cannot pass forwards because the pretracheal fascia and the superficial layer of the deep fascia seal off the retrovisceral space from any communication with the anterior mediastinum Below the level of the hilum of the lung pus coming from a perforation of the oesophagus can track forwards around the pericardium between it and the pericardial pleura it may also pass upwards or down through the oesophageal hiatus of the diaphragm into the retroperitoneal space in the abdomen



(*b*) Diagrammatic transverse section of the neck at the level of the sixth cervical vertebra The retrovisceral space is depicted in red and the heavy black partitions represent the principal fascial membranes Note that the oesophagus is closely applied to the back of the trachea but that there is a space (shown in red) containing loose areolar tissue between it and the prevertebral fascia This space is limited anteriorly that is immediately behind the oesophagus by a condensation of the areolar tissue known as the bucco-pharyngeal membrane This membrane is closely applied to the back of the gullet and fuses with the carotid sheath laterally The result is to create a closed space from which pus cannot pass forwards but can pass up or down the neck The retrovisceral space is not divided into right and left halves but is continuous from side to side

PLATE IV



This painting is made from an anatomical specimen It represents half the neck of an adult at the level of the body of the sixth cervical vertebra The specimen has been mounted so that it hangs from 2 strings attached anteriorly and the weight of the vertebra and neck muscles pulling downwards has opened out the tissue planes spontaneously Note the manner in which the oesophagus has remained firmly opposed to the back of the trachea Note also that an artificially created space (the retro visceral space) has appeared behind the oesophagus in front of the prevertebral fascia and medial to the carotid sheaths This space is the one in which suppuration occurs and spreads if the oesophagus be perforated The anatomical relations of an abscess in the retrovisceral space are clearly shown

the detection of crepitus in a particular place does not mark out the tissues infected by bacteria

The organisms which produce the most virulent type of cellulitis are anaerobic streptococci and staphylococci or the bacteria found in Ludwig s or Vincent s angina They generally come from infected teeth or from tartar and they cause a rapid haemorrhagic oedematous necrosis of tissue The destruction is increased in perforations involving the lower oesophagus by the acid and pepsin regurgitated from the stomach which add a chemical to the bacterial inflammation

The site of a perforation has a bearing upon the outcome The effects of a cervical perforation are most obvious in the neck but they practically always involve the superior mediastinum as well If the gullet be perforated near the diaphragm it is unusual for the inflammation to spread upwards above the hilum of the lung although it may pass down through the oesophageal hiatus or separate the parietal pleura from the pericardium The paths which inflammation follows are controlled by anatomical structures this aspect was first studied by Furstenburg (1929) and has been reviewed more recently by Neuhof and Jemerin (1936 1939 1943) The relevant anatomical points are that the oesophagus from the larynx to the cardia is enveloped in loose areolar tissue which permits easy extravasation Cervical perforations practically always open into the retropharyngeal or into the retro visceral space which lies behind the gullet between it and the prevertebral fascia This space which extends outwards in the neck as far as the carotid vessels and upwards to the base of the skull is continuous with the superior mediastinum and thence with the posterior mediastinum Anatomical barriers betwe n the neck and the superior mediastinum do not exist An inflammatory process which has attained the retrovisceral space in the neck can pass downwards in this space into the mediastinum It cannot get into the anterior mediastinum because it is confined behind the pretracheal fascia which is itself attached to the coverings of the aorta and to the top of the pericardium Inflammation is directed downwards behind the oesophagus as far as the level of the bifurcation of the trachea where it is generally contained By contrast a perforation of the lower oesophagus induces inflammation which spreads upwards in the posterior mediastinum encircles the gullet and because the pretracheal fascia does not exist at this level passes forwards around the pericardium towards the lower parts of the anterior mediastinum The posterior and the superior mediastina are divided into right and left halves by the trachea the great vessels and the heart The right sided compartment is the bigger but collections of pus on either side displace the viscera towards the opposite side

Other factors contribute to the serious condition which occurs with mediastinitis Throughout the neck and the thorax there are extensive interwoven lymphatic channels which play a role in determining directions of spread and which make it theoretically possible for infections to travel almost anywhere in the area Moreover the cardiac movements which impinge continuously upon the oesophagus as it traverses the posterior mediastinum help to disseminate exudates and pus The oedema the inflammatory exudates and the pus which are often contained within tightly stretched pleural membranes on either side of the posterior mediastinum are under positive pressure which has a harmful effect upon the circulation because it disturbs the return of blood through the great veins to the heart Several surgeons have noted that when the mediastinal pleura is incised and

the pus has gushed out there is an improvement of the systemic blood pressure and a fall in the venous pressure as well

Diagnosis of perforation of the oesophagus

Diagnosis and treatment involve two problems In one group of patients the surgeon is faced with an emergency which is suspected or known to have occurred within the last few hours he will be asked to prevent or to control spreading cellulitis of the mediastinum In other patients seen for the first time some days after the perforation has occurred the problem is to detect locate and treat an abscess

The acute emergency —The only circumstance in which a surgeon is likely to diagnose an injury as soon as it has happened is when an endoscope has been pushed through the wall of the gullet For the rest he is dependent upon his ability to piece together a history of an accident which might have caused an injury with signs symptoms and radiological findings which are suggestive and if life is to be saved it may be necessary to embark upon active intervention before positive proof is available

The earliest symptom of cervical perforation and one which often appears within 6 hours is pain in the neck or the chest accentuated by attempts to swallow it is severe and is increased by movements of the larynx coughing and deep inspiration Other symptoms which may be present in various combinations are salivation dysphagia fever dyspnoea and a sensation of something sticking into or pricking the throat Deep surgical emphysema is not always present but clinches the diagnosis if crepitus can be found Oedema and tenderness felt most obviously along the borders of the sternomastoid muscle are valuable signs

Acute perforations in the mediastinum are characterized by rapidly developing toxaemia Local signs are not likely to be found but surgical emphysema can sometimes be palpated in the suprasternal notch or in the posterior triangles of the neck The patient often has great abdominal pain and rigidity Vomiting is usual at the outset but is not continuous because as the mediastinal spaces open up the gastric contents are discharged around the oesophagus or into the pleural cavity There is a rapid pulse collapse and great distress The patient often prefers to sit and may ask to be held in a forward position The respirations may be shallow rapid and grunting and cyanosis has been observed The differential diagnosis is from perforated peptic ulcer of the stomach or the duodenum myocardial infarction dissecting aneurysm of the aorta acute pancreatitis and possibly from a fulminating coccal infection of the kidney

The radiological signs in the neck are collections of air or bubbles of emphysema in the tissues the presence of a foreign body in some cases and a widening of the retrovisceral space which in the lateral films of the neck is clearly shown In the mediastinum the significant points are surgical emphysema depicted either as bubbles or as a clear halo immediately outside the pericardium widening of the mediastinum and occasionally a fluid level can be discerned In doubtful cases a small barium swallow may define a perforation but only positive findings are relevant

Oesophagoscopy may be necessary to confirm the diagnosis and to locate the anatomical position of the injury



Fig 67.—Radiograph of the neck of a woman whose oesophagus had been perforated in the manner described by Goligher (1948). Note the abscess in which there is a fluid level in the retrovisceral space which has displaced the gullet and the larynx forwards. Below the fluid levels bubbles of surgical emphysema can be seen. This abscess which extended far down into the mediastinum was successfully drained through a cervical incision.



Fig 68.—Radiograph of the neck of a patient who had swallowed a piece of mussel shell 3 days previously. The fragment is impacted in the lumen of the oesophagus immediately below the crico-pharyngeal sphincter. Note that the gullet is not displaced forwards.

Treatment of acute perforation of the oesophagus —There are certain principles which apply to this topic When the oesophagus has been perforated the position is critical and whether active or expectant measures be adopted the patient should be prevented from drinking until the defect has closed or has been closed Antibiotics and chemotherapy should be used in all serious inflammations but there is no good evidence as yet that the prognosis of this group of cases is strikingly improved by this treatment alone and the question of whether to operate must not be influenced by the availability of these drugs Most surgeons are agreed that unless a perforation has obviously localized spontaneously at the time the patient is first seen the treatment is prompt operation The following statistics support these statements

Phillips (1938) reported the histories of 20 patients whose gullets had been perforated by various endoscopic manipulations Early surgery was practised in all 3 died and in 2 the cause of death was faulty surgical technique By comparison with this series there are others in which the mortality of expectant treatment ranged from 50 to 100 per cent although every surgeon has had personal experience of isolated cases in which complete recovery has occurred without treatment Jemerin (1948) analysed 69 cases of suppurative mediastinitis due to a variety of conditions he had already contributed an important review of this subject with his colleague Neuhof (1943) and they stated that the mortality in patients treated conservatively before 1936 was 77 3 per cent whereas after that date when practically all underwent operation it was 17 per cent Penicillin and other antibiotics were not considered to be the main cause for this improvement Adams (1946) of Boston Dorsey (1948) and others concurred with these observations

The requirements at operation performed in the phase of cellulitis or before infection has occurred are to expose and close the perforation in the simplest possible way and to drain the retrovisceral space either in the neck or through the pleural cavity

Cervical perforations including those in which the pus has tracked down into the superior mediastinum can practically always be effectively treated through a single cervical incision The perforation in the oesophagus should be closed under local anaesthesia and the wound packed loosely with gauze to maintain drainage Antibiotics should be applied locally and the patient fed through a small indwelling plastic catheter or by intravenous therapy Gastrostomy is not necessary In some cases a temporary fistula will develop but provided the inflammation has been controlled this can be ignored

The same principles apply to the treatment of mediastinal perforations but the situation is complicated because access must be had across the pleural cavity which may be uninfected at the time A general anaesthetic and a lateral thoracotomy are indicated At the end of the repair of the oesophagus the mediastinum must be drained into the pleural cavity and from then onwards the patient is treated as though he had an acute total empyema The surgical details are mentioned in the section of this chapter concerning spontaneous perforation of the oesophagus

Diagnosis and treatment of perforations seen several days after the event —In this type of case the perforation has been missed at the time and the patient has been fortunate to live and to localize the inflammation The onset of symptoms is not

dramatic and the diagnosis is often delayed A typical example is the patient who having had an oesophagoscopy complains of pain some hours later The pain is generally localized to one spot and is accentuated by movements coughing deep breathing and attempts to swallow In the neck an oedematous deeply placed mass may be palpable but the abscess extends to the upper mediastinum The fascial planes described above prevent the pus from coming to the surface There may be pyrexia and other signs of inflammatory toxaemia but the general condition may be good at first Hiccup is an occasional and a distressing symptom The diagnosis may be further suggested by radiography and is certain if a small barium swallow shows a tortuous extra oesophageal track but oesophagoscopy is eventually essential in most cases to prove the presence of a perforation and to exclude pre existing diseases such as a diverticulum a carcinoma or a perforated peptic ulcer due to reflux oesophagitis

The treatment of the patient who is seen late depends upon the clinical state In some expectant treatment and suitable antibiotics enable the patient to achieve his own cure but if the clinical radiological and symptomatic improvements are not progressive surgical drainage of the abscess becomes necessary In the neck the operation is straightforward and in the thorax a costo transversectomy done under general anaesthesia will be needed The pleural cavity should not be opened

Concerning certain late complications of perforation of the oesophagus—A fistula between the gullet and the skin behaves as does a fistula in any other part of the alimentary canal that is it closes spontaneously in due season without the necessity for surgical intervention provided that there is no distal obstruction to the lumen of the gullet and no retained foreign body in relation to the track

The treatment of tracheo oesophageal fistula is more difficult for this lesion is apt to persist It complicates those wounds and penetrating pathological lesions which involve the gullet and the trachea or larynx and is intolerable to the patient because swallowed liquids and foods pass into the air passages causing paroxysms of coughing and recurrent pneumonitis As time passes stenosis of one or both tubes complicates the issue Surgical treatment is essential and involves an operation to separate the trachea from the gullet and some form of plastic procedure to replace a gap after excision of a stenosis Until recently the accepted method of doing the latter was to turn in skin flaps using some modification of the old operation devised by Trotter (quoted by Thomson and Negus page 787 (1948)) More recently Rob (1949) has successfully replaced portions of the trachea and the oesophagus by filling the hole with a plastic tube covered with a fascia lata muff and Belsey (1950) has replaced segments of the trachea with a wire spiral covered with a similar muff

A fistulous track from the mediastinal oesophagus to the pleural cavity produces an empyema which is difficult to treat because swallowed matter is discharged into the pleural cavity tending to perpetuate the empyema and to starve the patient of food and drink The empyema must be drained by rib resection and closed drainage In these chronic cases feeding is difficult and a gastrostomy or a plastic catheter passed from the nose to the stomach may be necessary An operation to close the hole in the oesophagus should not be done across the chronic empyema Sutures so placed always slough out and in any event the hole will eventually close spontaneously The chronic empyema will then require surgical treatment The most

complicated cases are those in which there is a fistula between the oesophagus and the lung The patients are generally ill wasted and toxic they cough when they take food and they expectorate unpleasant sputum The pleural cavity has generally been shut off but the affected lobe of the lung is closely adherent to the gullet The necessary investigations are bronchoscopy and oesophagoscopy a barium swallow and bronchography these are to determine not only the exact anatomy of the fistula but whether or not the affected lobe of the lung has been permanently destroyed by suppuration In most cases treatment consists of thoracotomy separation of the oesophagus from the lung repair of the oesophagus lobectomy and drainage of the mediastinal and pleural spaces This operation is well tolerated provided proper facilities for anaesthesia and continuous resuscitation are available

In sharp contrast to the difficult operations and the prolonged illness imposed by these serious late complications is the easy convalescence of the patient in whom a perforation of the gullet has been surgically repaired within a few hours of the accident

SPONTANEOUS RUPTURE OF THE NORMAL OESOPHAGUS

Until recent years this condition was always regarded as rare impossible to diagnose and fatal It was first described by Boerhaave in 1723 and since then many case records have become available (Barrett 1946 Eliason and Welty 1946 Kinsella and others 1948) Modern writers have stressed that there is a characteristic symptomatology which should lead to a correct diagnosis and early surgical treatment The first successful operation was reported by Barrett in 1947 and others have since been performed by Olsen and Clagett (1947) and by Lynch (1949)

Definition —The lesion under consideration differs from other ruptures of the gullet in that there is no pre existing disease or cause such as external violence or penetrating injury and consequently nothing in the previous history directs the attention of the surgeon to the oesophagus Some cases of peptic ulceration or growth of the oesophagus are clinically silent and may rupture unexpectedly into the mediastinum in these the result may be the same as in spontaneous rupture of the normal gullet though the cause is different The emergency treatment is the same

Incidence —More than 100 undoubted cases have been recorded the majority in recent times Men are more likely to be afflicted than women and although children are not immune the usual age period is between 35 and 55 years

The cause —In a small number there is no apparent reason why the oesophagus should have ruptured but in the majority the cause is persistent serious retching or vomiting This has occurred in alcoholics after heavy meals in various toxaemias in epilepsy in sea sickness and as a result of impaction of food in the oesophagus above the cardia

Pathology

The rupture is situated immediately above the diaphragm Mackenzie (1884) was one of the first to explain the site and mechanism he pointed out that the rupture was practically always a longitudinal tear although in Boerhaave s original case and in a few others the oesophagus was transected completely and the ends drawn apart He showed that the lower third was the weakest part of the oesophagus

that a spontaneous rupture never occurred in the upper oesophagus that the left side was more often involved than the right and that in the early case there was no inflammation to suggest pre existing disease—in fact it looked as though the wall of the gut had been cut open with a sharp knife The cause of the tear was a sudden increase in the pressure inside the gullet resulting in an immediate expulsion of gastric and oesophageal contents into the mediastinum or the pleural cavity air is also expelled so that surgical emphysema may be expected early The effect of this extravasation is to produce a fulminating chemical and bacteriological cellulitis which seldom localizes spontaneously and which generally kills the patient if untreated within 48 hours The predominant organisms are anaerobic germs from the mouth Although haematemesis is uncommon blood stained fluid and oedema are always present in the mediastinum The liquid in the pleural cavity is at first gastric contents but this is soon augmented by a profuse inflammatory exudate so that the pleura itself exhibits the most striking range of colours and may eventually contain as much as a gallon of sour odorous liquid

Signs and symptoms —In practically every case the onset is dramatically sudden and leads immediately to a state of acute emergency The patient who is conscious and who is vomiting or retching experiences such an excruciating pain that he feels that his heart must have burst In some the pain is centred upon the xiphoid process in others it shoots through to the back or strikes in the left shoulder Excruciating in character unrelieved by drugs rest or movement it persists until death The complexion becomes ashen grey with perhaps a tinge of cyanosis and the patient is restless anxious and very thirsty The t mperature is at first sub normal but soon begins to rise the blood pressure is low and the pulse rapid the brow is moist with perspiration There is usually rigidity of the upper abdominal wall and the signs suggest a perforated gastric ulcer or myocardial infarction The most significant features of ruptured oesophagus are cyanosis grunting respirations surgical emphysema at the base of the neck persistent pain in the lower thorax and rigidity of the abdominal wall

Within 6 hours of rupture air and oedema may be palpable in the tissues of the base of the neck but there may be few signs to suggest pleural involvement On several occasions the radiologist—looking for air below the diaphragm because a perforated gastric ulcer had been suspected—has seen air or liquid behind the heart or in the pleural cavity Taken in conjunction with the other points these radiological findings are diagnostic but if further proof be needed a small amount of radio opaque oil may be swallowed Aspiration of liquid from the pleural cavity will also help for it contains hydrochloric acid

Treatment

It is practically certain that untreated the patient will die within a few days but there are a few records (Graham 1944 Moore and Murphy 1948) in which localization occurred spontaneously or in which conservative surgery (such as pleural drainage or jejunostomy) succeeded after long and dangerous illnesses Scrutiny of these accounts and of the more numerous others in which failure and death resulted has convinced surgeons that immediate and early thoracotomy is indicated The goal is to repair the tear in the oesophagus to drain the mediastinum and to drain the pleural cavity These directions were first suggested by Collis and

others (1944) It is wrong to defer operation in the hope that supportive measures such as blood transfusion and morphine will improve the general condition of the patient Decompression of the tension pneumothorax (which is practically always present) by needle aspiration and suction intravenous fluid to satisfy the patient s thirst and intensive chemotherapy are indicated as soon as the diagnosis has been made and before the patient goes to the theatre If there is no clear pointer as to which side should be operated upon the surgeon should do a left low thoracotomy A general anaesthetic with intubation of the trachea is necessary As the pleural cavity is opened at operation gastric contents and effusion gush out if the mediastinum has already ruptured These may be sour in smell and contain particles of food and the pleural membranes are livid and highly coloured by inflammation By retracting the lung the tear in the lower mediastinum can be discerned behind and parallel to the pulmonary ligament This rent must be opened and a cavity will be found containing bloody fluid food particles and pus disposed in the oedematous tissues of the mediastinum When these extraneous substances have been sucked out and the mediastinal excavation debrided the surgeon then sees the oesophagus traversing the bottom of the space and the anaesthetist often reports an improvement in the condition of the patient This is due to relief of the tension pyopneumothorax the improvement in ventilation and to the rise in blood pressure which occurs as a result of mediastinal decompression The hole in the oesophagus should be sutured in the simplest and quickest way and as the edges of the tear look and feel like wet chamois leather, no attempt at complicated inverting stitching is worth while (*see* Fig 66) The mediastinal pleura should be spit from the top of the thorax to the bottom thus establishing free drainage into the pleural cavity and the mediastinum liberally dusted with penicillin and streptomycin powder The pleural cavity itself should be drained with a water seal apparatus and chemotherapy continued as may be necessary The thoracotomy incision should be closed without drainage for it will heal by first intention and the patient should be given a liquid diet for the first few days

PERFORATION OF THE GULLET BY INTUBATION OESOPHAGOSCOPY OR GASTROSCOPY

Endoscopy and intubation of the trachea performed for anaesthesia diagnosis or treatment carry a definite though small risk that the gullet may be perforated Several different types of accident have been described and because the prevention and treatment of each varies it is worth considering the possibilities separately

A small tear of the mucous membrane of the pharynx (Georg 1917 Luke 1913) can lead to one of the most dramatic catastrophes in surgery Two typical cases were reported by Barrett and Thomas (1944) Both occurred in young patients (one of whom was having an appendicectomy and the other a bronchogram under general anaesthesia) The accidents were caused by introducing an airway into the mouth in such a way that the mucous membrane at the back of the pharynx was torn The tears were so trivial that at first they passed unnoticed and the anaesthetist proceeded to give oxygen and gas under slight positive pressure to maintain anaesthesia All went well until it was noticed that the eyelids and face were oedematous Within a few minutes the swelling spread it was crepitant and due to surgical emphysema The emphysema increased rapidly and the patients

became unrecognizable as human beings so great was the distortion of the normal body contours The air tracked subcutaneously all over the body and one of the patients (untreated) died of asphyxia in a few minutes It was the impression that the initial emphysema was due to the anaesthetic but that as these were discontinued in both cases as soon as the puffiness of the eyelids was noted and as the emphysema continued to increase afterwards the subsequent developments were probably caused by increased inspiratory efforts made by the patients in an attempt to overcome the increasing obstruction to the airway At autopsy diffuse emphysema was found throughout the subcutaneous tissues in the planes of the neck and the mediastinum the pharyngeal tear was so slight that it would not have been found without special search

Treatment must be prompt Remove the airway from the mouth and replace it by a wide bore tracheal tube start artificial respiration provide oxygen with a face mask and without positive pressure try sucking the air out of the neck through a large needle and if this does not produce relief incise the deep fascia at the base of both posterior cervical triangles and above the sternal notch and massage the air out of the deep tissues of the neck

Another cause of perforation is unskilled attempts to pass an instrument into the entrance of the oesophagus against spasm or resistance of the cricopharyngeal sphincter Spasm occurs under local anaesthesia when the patient is nervous or when the instrument is passed with the patient s head and neck in a faulty position it occurs with attempts to remove a foreign body impacted in the upper reaches of the oesophagus or as a result of previous unsuccessful attempts to pass an endoscope it is often due to bad anaesthetic technique To pass an endoscope into the gullet without danger the patient must either have been given complete local anaesthesia of the larynx and pharynx or a general anaesthetic to relax the cricopharyngeal sphincter absolutely that is deep general anaesthesia or curare and controlled respiration

Fletcher and Avery Jones (1945) drew attention to a hazard which was not uncommon when rigid gastroscopes were in vogue but which has been eliminated by the use of the flexible gastroscope I refer to traumatic perforation of the post cricoid region of the gullet This accident is most usual in elderly patients in whom an oesophagoscope has been passed without difficulty it has no connection with spasm of the cricopharyngeus The lesion is always a longitudinal tear any thing up to an inch or more in length extending through the mucosa and muscle coats and situated in the upper reach of the gullet In the past it had been assumed that the cause was a direct acute injury caused by the beak of the instrument and in that particular place because owing to the dehiscence of the longitudinal muscle fibres the circular fibres were unsupported Prior to these observations Taylor (1945) had stressed the intimate anatomical relationship which obtains between the front of the cervical spine and the back of the gullet and that the anterior surfaces of the cervical vertebrae were ridged at the top and bottom of each vertebral body With the neck extended the gullet was stretched out over this bony arch a fact which can easily be verified in the autopsy room when the body lies flat on the table and the oesophagus has been lifted out Mosher (1935) had emphasized that in old people intraoesophageal protrusions could be produced by osteophytes due to osteoarthritis Goligher (1948) (*see* Fig 67) assembling these arguments stated

that by hyperextending the head and passing an oesophagoscope the back wall of the upper oesophagus could be nipped in the mid line between the instrument and the protuberance formed by the lower cervical spine The tear produced was due *to pressure necrosis and the effects might be delayed several days until the necrotic* tissue had separated and a leaking perforation had occurred The results of such a perforation were more likely to be a perioesophageal abscess than a fulminating cellulitis My experience tallies closely with that of Goligher and I subscribe to his explanation and treatment namely early surgery to repair the tear in the oesophagus and to drain the fascial planes of the neck

Perforation has caused death of patients suffering from oesophageal stricture (simple or malignant) and has been due to attempts to engage an endoscope *graded bougies or a hydrostatic dilating bag in the stricture Do not dilate* any oesophageal stricture unless a filiform gum elastic guide can first be passed or unless the patient has previously swallowed a string The latter is a wise precaution the night before oesophagoscopy the patient should be told to swallow one end of a piece of coloured string to which a lead shot has been attached the other end should be fixed to the cheek At oesophagoscopy the coloured string can be followed and instruments certainly guided into the narrowed lumen rather than into diverticula or folds of mucous membrane above the block Ruptures of this *type are either due to pushing an instrument through the gullet above the block* or to rapid dilation and splitting of the stricture itself

Gastroscopy carries a risk of perforation and Avery Jones and others (1951) have recently reviewed this subject They collected a series of 49 000 examinations which had been done by 40 different gastroscopists and found that in this large group of cases only 75 accidents had occurred In the early days of gastroscopy perforation of the stomach or even of the duodenum and jejunum was more common than oesophageal injury but in this modern series there were 54 *oesophageal injuries and only 9 perforations of the stomach*

Two thirds of the perforations involving the gullet occurred at the upper end or in the pharynx and the gravity of the accident is underlined by the finding that nearly half the patients died A number of other observations which have a bearing on prophylaxis were made Nearly every perforation was caused by using the Hermon Taylor instrument as opposed to that devised by Wolf Schindler thus

Hermon Taylor gastroscope	*14 000 examinations*	22 perforations
Wolf Schindler gastroscope	9 000 examinations	1 perforation

In most cases where perforation had occurred there had been no difficulty in passing the instrument (*see* Goligher s observations above) and analysis of the figures by age and sex led to the important finding that the risk in women over 50 years of age was 10 times higher than in a corresponding group of men and 30 times greater than in young men

Avery Jones recommends *that accidents* can be reduced by a preliminary barium swallow and radiological examination of the spine to detect unsuspected oesophageal stricture or kyphosis He states that perforation of the oesophagus could be practically eliminated by giving up the use of the Hermon Taylor gastro

scope The instrument has however great practical advantages and provides a more certain view of the distal part of the antrum and the posterior wall of the stomach For this reason it may be preferred for operations performed upon young men but should be discarded in the case of women over 50 years Another practical point about which all gastroscopists agree is that it is essential in passing the instrument to maintain flexion of the head and to use the fingers to keep the tip of the instrument from impinging upon the posterior wall of the pharynx Using this technique Hermon Taylor has performed several thousand gastroscopies without perforation of the gullet

Some patients recovered spontaneously from the accident without operation but if the mortality is to be reduced from 50 per cent early operation must be carried out in every patient except those few in whom careful clinical observation shows that localization has occurred

INJURIES CAUSED BY SWALLOWED CORROSIVES

Corrosives may be swallowed accidentally in which case lye is the most common or with intent of suicide when acids such as carbolic nitric or hydrochloric are drunk Lye contains sodium hydroxide in a concentration of 95 per cent and thus like many other household cleansing agents is strong enough to be a dangerous poison The harmful effects of corrosives depend upon their concentration and upon the amount swallowed Death for example can occur within a few hours or the burns in the gullet may be so trivial that the serious symptoms are never manifest

Pathology

In patients who survive the injuries are usually limited to areas of linear necrosis of the mucous membrane which heal rapidly and which may cause no harmful effects When the burns are more severe the muscle coats or the perioesophageal tissues and the pleura can be involved and if the victim does not die of mediastinitis or its complications there is a tendency for strictures to develop in the post cricoid region at the place where the left bronchus crosses the gullet or at the lower end The dead tissues are shed as sloughs into the lumen of the oesophagus from the second week onwards Granulation tissue remains and leads to a contracting scar If the destruction has not been too extensive the scar is limited to a band of tissue which never returns to normal but remains contracted avascular smooth and devoid of mucous membrane Grey Turner (1946) laid stress upon the fact that during the first days after the accident the whole gullet is weakened and soft as a result of oedema and inflammation and that in consequence endoscopic treatment or bouginage carries a dangerous risk of perforation He considered that the weakness persists for weeks and that it modifies treatment Dysphagia may not occur for several months

Symptoms—Swallowing of a corrosive produces immediate severe pain in the mouth the pharynx and in the gullet Salivation is stimulated but within a few hours the patient is often prevented from swallowing so that saliva and fluid taken to quench thirst must be rejected Soon after the injury inspection of the mouth and pharynx reveals ulcerous patches covered with sloughs of white necrotic mucous membrane Odynphagia may be intense The acute symptoms persist for

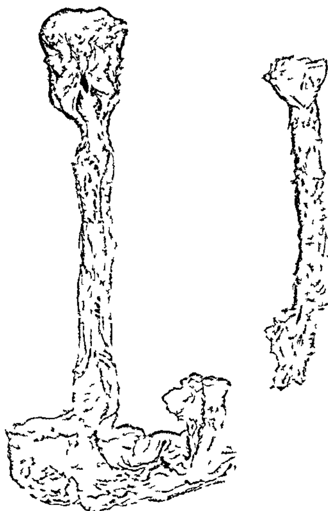


FIG 69 —The pharynx oesophagus and stomach of a man who swallowed several ounces of strong caustic potash and who lived for 3 months A week after the accident the mucosal cast shown on the right was found protruding from his *mouth after a severe bout of retching It was drawn out and* cut off Increasing dysphagia occurred until he died 2½ months later At that time the gullet was still practically denuded of epithelium and much inflammation persisted

several days but by the end of a week they have generally subsided and the patient may appear to be cured

Vomiting a cast of the oesophagus is a well recognized sequel which may happen at about this time The condition was called oesophagitis dissecans profunda by Kaufmann (1911) because the tissue discharged often contained parts of the muscle coats as well as the necrotic mucosa Some casts were 20 to 30 centimetres in

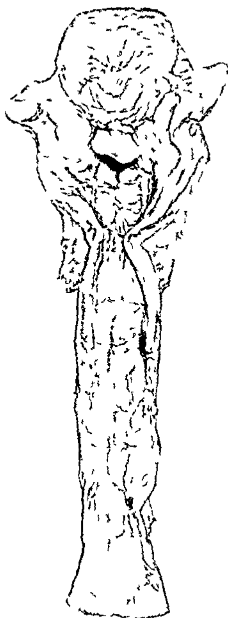


FIG 70 —The tongue larynx and gullet of a patient admitted in a comatose condition and smelling strongly of Lysol The tongue the mouth the oesophagus the stomach and the upper part of the small bowel were covered with a white sloughing membrane and the whole of the mouth and larynx were very oedematous She died of respiratory obstruction at the level of the larynx

length but more usually sloughs were disgorged piecemeal (*see* Fig 69) In the patient who appears to be convalescent at the end of a week a latent period may follow and during the next 6 to 9 weeks there may be no dysphagia and no untoward effects the fact that medical men are not familiar with this respite has resulted in strictures which might have been prevented Dysphagia may thus be due to spasm soreness or oedema in the acute phase to granulation tissue in the convalescent period and to a fibrous stricture after 6 weeks

Treatment

If the patient is seen soon after the corrosive liquid has been swallowed it is worth attempting neutralization In lye poisoning Crowe (1944) recommends slow oral administration of large amounts of dilute vinegar together with olive oil Gastric lavage makes little difference and is theoretically dangerous For acids sodium bicarbonate serves Other treatments in the acute stage include supportive measures to deal with shock analgesics to alleviate pain and emollients for the buccal and pharyngeal burns If absolute oesophageal obstruction due to oedema develops a temporary gastrostomy and intravenous therapy may be necessary to tide over the acute phase As soon as the patient can drink without pain or at the end of the first week when the acute inflammation should have subsided a long string fixed proximally to the cheek should be swallowed and kept in place during the following 6 weeks This ensures that if stricture develops a lumen will be maintained Treatment is thenceforth directed to preventing a stricture and experience shows that this can be achieved if the patient swallows a mercury loaded eyeless catheter at regular intervals (In the literature this treatment is often referred to as Bokay s method (1942)) Active dilatation should start at the end of the first week using no force and allowing the loaded catheter to find its way into the stomach by its own weight At first a small catheter should be used (size 10–30 French) and the manoeuvre repeated daily for about a fortnight the size of the instrument is then increased and the intervals of treatment spaced out a little There is no need for oesophagoscopy during this period and most surgeons consider such an investigation dangerous but there is much in favour of a small barium swallow so that serial radiographs may be available This in fact is the only way of controlling and directing treatment

Patients of all ages still come to the surgeon with established strictures and in them no attempt has been made to avoid the catastrophe the usual treatment has been gastrostomy In England Grey Turner (1939 1940) has done more than anyone to show the best ways of handling this difficult problem He believed that however complete obstruction may seem to be there was always a tortuous track through the block and that this track could be found by patient endeavour He advocated the treating of strictures by the method he called self bouginage and he quoted many successes to support his belief In essence this treatment depends upon the surgeon managing to pass the stricture often using the finest bougie at first and having established a small fairway the patient is then taught to swallow graded bougies at regular intervals The golden rule is never to employ force or roughness and never to cause pain Other surgeons such as Moersch at the Mayo Clinic and Negus in England have preferred to dilate fibrous strictures endoscopically This can be done with a hydrostatic dilating bag introduced into

the obstruction through an oesophagoscope or if the patient has a gastrostomy already by retrograde dilatation from the stomach using a continuous thread from the mouth to the gastrostomy opening and olive shaped metal dilators strung like beads on the thread It is seldom necessary or advisable to do a gastro stomy Leary (1949) stated that Moersch had treated 115 patients endoscopically with Plummer s bag and no death attributable to treatment had occurred A five year follow up in 57 of these patients showed that only one had serious persistent dysphagia and five had some difficulty in swallowing "The treatment is generally prolonged requiring several months Even then the patient must return at regular intervals for years to be certain that the stricture is not reforming The writer elects to dilate strictures by introducing graded laminaria tents through an oesophagoscope but whatever method be preferred the same principles obtain as govern the management of urethral stricture and treatment which stretches the constriction so quickly as to produce obvious trauma defeats its own ends

The indication for resection of a benign stricture of the oesophagus is failure of dilatation at the hands of an expert Excision of the stricture and re-establishment of continuity has been advocated by Yudin (1944) who reported surgical treatment of 80 patients by stage operations in which he brought up a loop of jejunum in front (subcutaneously) of the thoracic cage and anastomosed this to the oesophagus in the neck above the stricture This operation is obsolete and has been replaced by excision of the stricture and anastomosis in the mediastinum This was developed by Sweet (1946) Garlock (1948) and others who devised the technique for resecting the oesophagus mobilizing the stomach and anastomosing it to the oesophagus at any level in the mediastinum or the neck This operation has the disadvantage of removing the cardia and thus allowing reflux of gastric contents for this reason it encourages the development of oesophagitis To overcome these drawbacks Gross (1948) following the lead of Holt and his associated (1946) who had performed 26 successful anastomoses of the oesophagus itself in babies suffering from congenital atresia recommended and practised local excision of the stricture with immediate anastomosis of oesophagus in the mediastinum This operation is only practicable in those cases where the stricture is short but one often finds that although the main stricture may be restricted in length there is above it an inflammatory fibrosis which may extend for a considerable distance

Idiopathic oesophageal casts

The casts of the oesophageal mucosa and muscle described above are composed of necrotic tissue caused by the swallowing of corrosives or by burns There is another variety of oesophageal cast which is different and the literature upon this subject has been reviewed by Patterson (1935) The first recorded case was accurately described by Birch Hirschfeld (1877) and since that time about 25 examples have been put on record In their clinical details and progress these patients have behaved in a way which is so characteristic that the condition can almost be regarded as a syndrome A patient recently reported by Willcox (1949) is typical A woman aged 40 produced 4 oesophageal casts over a period of 15 years She had always been a fit person and relevant physical examinations were negative There was no history of trauma nor the swallowing of corrosive but on each occasion a cup of tea had been drunk shortly before the production of the casts The patient first noticed a

burning sensation in throat and epigastrium and this was associated with marked salivation Soon afterwards there was pain on swallowing and the saliva appeared to stick halfway down the gullet She then vomited up a tube of tissue which hung from her mouth and remained attached at the back of the throat The events were the same on each occasion except that once the tube was pulled off once cut off and once bitten off Every time convalescence lasted about a week and in the intervals there was no abnormality referable to the gullet

The reported cases range from infants to old people and the majority attribute the affair to the drinking of tea which was too hot or to strong alcohol The aetiology is unknown The sexes are equally affected and the condition is not connected with syphilis or any known inflammation it has nothing to do with diphtheria for example The tissue shed may be part or the whole of the mucosa of the oesophagus and the pharynx (Jacob 1916)

Sclavunos (1893) was the first to point out that the flimsy thin walled collapsed tube of tissue which had been vomited was inside out and that it consisted of squamous epithelium The initial lesion must be at the lower end of the gullet and is probably a circumferential necrosis which allows separation between mucosa and muscularis It is difficult to believe that the whole mucosa is shed because it is known that within a few weeks the gullet is completely lined by normal epithelium Once separation has started it is assumed that the process is accentuated by contractions of the musculature attempting to expel the foreign body from below upwards The nature of the initial lesion has remained in doubt Inflammation is absent in the specimens which have been examined histologically and the separating factor is thought to be oedema between the mucosa and the muscularis which produces a cast of tissue which is not necrotic Le Comte (1911) suggested that neurosis was the underlying factor and said the condition was reminiscent of membranous colitis The writer has seen a woman of middle age who came to the hospital bringing with her the cast of the oesophagus She was known to have had attacks of angio neurotic oedema which involved her face the mouth and the tongue An attack of angio neurotic oedema had not preceded the vomiting of the oesophageal cast but I wondered if the two events were connected Another suggestion was made by Sligh (1893) He had a patient a man aged 36 who every year since infancy had shed his whole epidermis including the finger and toe nails when the epidermis had peeled off there was good skin underneath Sligh believed that these oesophageal casts might simply be due to excessive exfoliation of squamous epithelium Alternatively the exfoliation may resemble that which occurs upon the surface of the body after streptococcal infections or scarlet fever

The patients make a complete recovery in a week to 10 days and no treatment is necessary Stenosis is not a complication and the barium swallows which have been done are normal 6 weeks later

FOREIGN BODIES IN THE GULLET

The fact that a foreign body often lodges in the gullet is well known but how to deal with the therapeutic problem is not so clear There are two aspects of this question namely obstruction and injury to the oesophagus the following remarks concern the latter although both disabilities often co exist Coins are most common

in adults and fish bones pins and small toys in children Lunatics and inebriates are apt to swallow objects which are too large to pass through the gullet and old people may lose their false teeth at night

The foreign body practically always sticks at the top of the gullet just below the

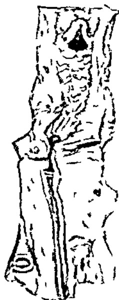


FIG 71 —The tongue pharynx and oesophagus of a child aged 4 months the child had swallowed a collar stud 8 days before admission to a hospital where unsuccessful attempts had been made to remove the foreign body The stud is in the lumen of the oesophagus and very little inflammation is present



FIG 72 —The larynx trachea and oesophagus of a child who one year before death had swallowed a 5-centime piece The coin lies in an abscess cavity which is outside the gullet but communicates freely with it There is a large mass of inflamed lymph glands adjacent to the abscess Death took place from broncho pneumonia the presence of a foreign body was not suspected during life

crico pharyngeal sphincter and if it passes this point it generally passes through the alimentary canal safely The probable explanation is that the musculature and hence peristaltic action is weakest at the top end of the oesophagus where the longitudinal fibres are deficient posteriorly Safety pins wire hair grips and other

burning sensation in throat and epigastrium and this was associated with marked salivation Soon afterwards there was pain on swallowing and the saliva appeared to stick halfway down the gullet She then vomited up a tube of tissue which hung from her mouth and remained attached at the back of the throat The events were the same on each occasion except that once the tube was pulled off once cut off and once bitten off Every time convalescence lasted about a week and in the intervals there was no abnormality referable to the gullet

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neck becomes swollen this sign does not mean that perforation has certainly occurred Lateral radiographs of the neck may reveal a foreign body or the manifestations of perforation and a lateral tomograph may define a piece of plate glass Whenever there is reasonable evidence an oesophagoscopy is indicated to confirm the diagnosis and this is especially true if the object lies in the mediastinal oesophagus for the signs are vague

Treatment

Negus observed that all foreign bodies entering by the mouth and arrested in the gullet should be removed by the same route and Chevalier Jackson (1945) said that no other methods are worthy of consideration He condemns all blind operations and groping manipulations carried out in the dark behind a fluorescent screen His experience is of more than 1 500 consecutive cases in which the objects were successfully removed through the mouth he reported one failure

The operations should be done under general anaesthesia in which full relaxation has been secured Adequate instruments for the task must be available and English surgeons generally prefer those devised by Negus They do not use complicated instruments such as those made for cutting rings breaking up tooth plates shutting safety pins because they believe that the dangers of using these tools outweigh their advantages In practice there are very few foreign bodies which cannot be safely extracted through an endoscope but there is still a necessity for removing some impacted objects surgically and the operations for doing this are well established and successful

REFERENCES

Adams R (1946) *J Thorac Surg* 15 336
Avery Jones F Doll R Fletcher C and Rodgers H W (1951) *Lancet* 1 647
Barrett N R (1946) *Thorax* 1 48
— (1947) *Brit J Surg* 35 216
— (1950) *Ibid* 37 416
— and Thomas D (1944) *Brit med J* 2 697
Belsey R (1950) *Brit J Surg* 38 00
Birch Hirschfeld F V (1877) *Lehrbuch der pathologischen Anatomie* p 818 1st ed Leipzig Vogel
Bokay J (1947) *Wien klin Wschr* 37 287
Collis J L Humphreys D R and Bond W H (1944) *Lancet* 2 179
Crowe J T (1944) *Amer J Dis Child* 68 9
Dorsey J M (1948) *Arch Surg Chicago* 56 24
Edwards A T (1943) *Brit J Surg* 31 74
Eliason E L and Welty R F (1946) *Surg Gynec Obstet* 83 234
Fletcher C M and Avery Jones F (1945) *Brit med J* 2 471
Furstenberg A C (1929) *Trans Amer laryng rhin otol Soc* 35 210
Garlock J H (1948) *Surgery* 24 1
Georg C (1917) *Amer J Surg* 31 77
Goligher J C (1948) *Lancet* 1 985
Graham E A (1944) Editorial comment *Year book of Surgery* p 382 Chicago Year Book Publishers Inc
Grey Turner C (1939) *Brit J Surg* 26 555
— (1940) *Ibid* 28 275
— (1946) *Oesophagus* p 39 London Cassell
Gross R E (1948) *Surgery* 23 735
Holt J F Haight C and Hodges F J (1946) *Radiology* 47 457

objects may impact above the cardia Apart from these natural obstructions one may find a foreign body such as a date stone lodged in a stricture a diverticulum, a new growth or in the dilated loop of gullet above an achalasia

Pathology

A foreign body seldom perforates the oesophagus until a surgeon tries to avulse it through an endoscope and there is no desperate hurry in attempting removal it will pay to hesitate and to study the problem Coins have lodged in the gullets of children for years without causing permanent harm and Thomson and Negus (1948) mention that a tooth plate was successfully removed after 18 years *Thus* there is a difference in the urgency of treatment between a foreign body in the gullet and suppurative mediastinitis (*see* page 226) the former is not harmless but in so far as it generally perforates slowly (unless it be driven through by manipulations) the locality becomes walled off by adhesions which prevent diffuse cellulitis There are a few records of spontaneous perforation having occurred into the neck, the mediastinum the pleural cavities the pericardium the great veins and into the left ventricle itself (Barrett 1950)

If a foreign body is retained for a long time it becomes impacted in vascular granulations which conceal it but it is rare for a fibrous stricture to complicate this accident The mucosa in the vicinity of a smooth body is unaffected by its presence for a long time because the wall of the gullet is flexible mobile and yields A small object may be hidden within the normal folds of mucosa below the crico pharyngeal sphincter and elude an inexperienced endoscopist Metallic objects soon turn black and coins or flat discs lie in the coronal plane of the body If perforation occurs it is *general for the foreign body to remain lodged in* granulation tissue in the wall of the gullet

If pulmonary symptoms develop the cause is overflow of secretion into the *trachea erosion of a foreign body into the trachea or main bronchi or trauma in* the larynx induced by attempts at removal

Diagnosis

Not all patients are aware that they have swallowed a foreign body and the majority of those who feel that a fish bone has stuck in the throat are not *correct in their assumption Many foreign* bodies are not discernible in radiograph and diagnosis is not easy in every case The problem is particularly difficult in infants and in old people and as the symptoms may not come on for several *weeks the physician may not consider the possibility Because of these uncertainties* every patient who believes he has swallowed a foreign body which has stuck must be investigated and those who in the course of other examinations are unexpectedly found to have retained foreign bodies should always be examined to eliminate the presence of other lesions such as carcinoma

The most typical pointers apart from the history are pain in the throat difficulty in swallowing due to spasm frothy saliva in the piriform fossae and oedema at the back of the larynx If lateral movements *of the larynx are painful it suggests* that an object has lodged in the upper oesophagus As time passes dysphagia increases until the patient may be unable to swallow saliva The temperature and pulse rate rise the voice *is affected by froth in the pharynx and* is coarse the

CHAPTER 11

RADIOLOGY OF THE OESOPHAGUS

A S JOHNSTONE

ALTHOUGH the oesophagus occupies a place so suitable for radiological study it appears to have suffered considerable neglect until the recent advances in thoracic surgery It is now no exaggeration to say that the oesophagus is the most frequently examined segment of the alimentary tract for not only is the examination essential for the investigation of disease of the upper alimentary tract but it forms part of the routine fluoroscopic survey of the heart In this chapter emphasis will be laid on the general examination and on certain abnormalities and diseases of the oesophagus which owe their recognition more to radiology than any other medical investigation Brief mention only will be made of some major disorders of the oesophagus which are described together with their radiology under separate headings

The normal oesophagus

The oesophagus is a hollow muscular tube about 25 centimetres in length and 1 25–3 centimetres in width It commences at the level of the sixth cervical vertebra and terminates opposite the eleventh thoracic vertebra The course of the oesophagus does not follow a straight line but takes a slight curve to the left at the root of the neck returning to the centre just below the arch of the aorta in the lower part of the thorax it makes a second curve to the left to enter the hiatal tunnel While passing through the tunnel it moves forwards as well as to the left At times this angulation is quite sharp and is considered by some observers to be a factor in preventing regurgitation

The walls of the oesophagus consist of four layers– mucosa with squamous lining submucosa muscularis propria and adventitia At the lower end the squamous epithelium joins abruptly with the columnar epithelium of the stomach The line of this junction is a matter of much interest there is no doubt that it is often irregular and may be found one centimetre or so above the termination of the oesophagus The submucosa is very loose and when belching occurs gastric mucosa appears to pass up into the oseophagus

Barrell (1950) in a recent paper contends that the oesophagus terminates with the squamous epithelium *He therefore considers that the terminal part of the* anatomical oesophagus if lined with columnar epithelium must be part of the stomach

The muscularis propria is thick and composed of striated and non striated muscle In the upper 6 centimetres or so it is striated muscle then there is a segment of mixed fibres and in the final 10–15 centimetres the muscle is non striated

Jackson C and Jackson C L (1945) *Diseases of the Nose Throat and Ear* p 746 Philadelphia Saunders
Jacob F H (1916) *Lancet* **1** 998
Jemerin E E (1948) *Ann Surg* **128** 971
— and Neuhof H (1939) *J Thorac Surg* **9** 1
Kaufmann E (1911) *Lehrbuch der Speziellen pathologischen Anatomie* 6th ed Berlin English translation by Reimann S P (1929) p 635 1st ed London Lewis
Kay E B (1947) *J Thorac Surg* **16** 207
Kinsella T J Morse R W and Hertzog A J (1948) *J Thorac Surg* **17** 613
Leary W V (1949) *Proc Mayo Clin* Sept 506
Le Comte A Jun (1911) *Ned Tijdschr Geneesk* **2** 1438
Lilienthal H (1926) *Thoracic Surgery* p 266 Vol 1 Philadelphia Saunders
Luke H C (1913) *Surg Gynec Obstet* **16** 204
Lynch J P (1949) *New Engl J Med* **241** 395
Mackenzie M (1884) *Diseases of the Throat and Nose* p 160 Vol 2 London Churchill
Moore J A and Murphy J D (1948) *J Thorac Surg* **17** 632
Mosher H P (1935) *Surg Gynec Obstet* **60** 403
Neuhof H (1936) *J Thorac Surg* **6** 184
— and Jemerin E E (1943) *Acute Infection of the Mediastinum* p 109 Baltimore Williams & Wilkins
Olsen A M and Clagett O T (1947) *Postgrad med J* **2** 417
Patterson T C (1935) *J Path Bact* **40** 559
Phillips C E (1938) *J Amer med Ass* **111** 998
Rob C G and Bateman G H (1949) *Brit J Surg* **37** 202
Sclavunos G (1893) *Virchows Arch* **133** 250
Sligh J M (1893) *Int med Mag* **2** 463
Sommer G N J Jun and O Brien C E (1948) *J Thorac Surg* **17** 393
Sweet R H (1946) *Surg Gynec Obstet* **83** 417
Taylor H (1945) *Brit med J* **2** 543
Thomson St C and Negus V E (1948) *Diseases of the Nose and Throat* 5th ed pp 787 810 London Cassell
Willcox J M (1949) *Lancet* **2** 417
Yudin S S (1944) *Surg Gynec Obstet* **78** 561

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Nerve supply

The vagi and sympathetic nerves supply the oesophagus with motor and inhibitory fibres Barclay (1933) stated that the vagal fibres for the upper part arose in the nucleus ambiguous while the lower part was supplied by the dorsal nucleus There is little doubt that radiologically the upper and lower segments of the oesophagus behave differently as might be expected in an organ which changes its musculature from the voluntary to *the involuntary type Gilbert and others* have shown experimentally in dogs that direct stimulation of the vagus nerves produced a marked contraction of the lower oesophagus which dragged the stomach into the thorax Similar changes followed stimulation of various abdominal viscera indirectly through the vagus This work however attractive it may appear, has not yet been sufficiently corroborated for acceptance

Anatomical relations

The principal anatomical relations of the oesophagus are few and can be summarized as follows

In the neck

The trachea lies anteriorly the lateral lobes of the thyroid are lateral and posteriorly are the prevertebral muscles and fascia

In the superior mediastinum

The trachea is anterior and the muscles and fascia overlying the upper thoracic vertebrae are posterior The oesophagus and trachea then pass behind the arch of the aorta and the descending aorta indents the oesophagus as it passes posteriorly

In the posterior mediastinum

The anterior relations are the bifurcation of the trachea the left bronchus the pericardium and the diaphragm The left auricle and part of the left ventricle are separated by the pericardium The clear space of *Holzknecht lies posteriorly be*tween the oesophagus and the vertebral column with its overlying structures Near the diaphragm the descending aorta passes immediately behind the oesophagus

As it leaves the thoracic cavity the oesophagus passes through the hiatus in the diaphragm which lies a little anterior and to the left of the aortic opening On entering the abdominal cavity the oesophagus unites with the stomach at the cardia Anatomists describe an abdominal part of the oesphagus about 1 5–2 centimetres *in length but this segment is rarely seen radiologically* Its existence is doubted by many surgeons and radiologists who feel that the anatomy found in the cadaver must differ from that seen *in vivo* (Fig 73)

The oesophageal hiatus

The hiatus in the diaphragm through which the oesophagus passes is formed principally by a gap in the fibres of the right crus These fibres present a broad edge on each side making a channel about 1 5–2 centimetres long Some fibres of the left crus can be traced to the right side of the hiatus and these interlace with the right crus anteriorly The left lobe of the liver lies anteriorly and may assist *in the occlusion of* the oesophagus when the diaphragm contracts

Surrounding the terminal 3 centimetres or so of the oesophagus is a fibro elastic sheath which is known as the phreno-oesophageal membrane This membrane arises from the under surface of the diaphragm around the hiatus and divides into ascending and descending parts The ascending part is inserted into the adventitia of the oesophagus about 2 centimetres above the diaphragm Its chief function is to prevent the stomach from being dragged into the thorax when the diaphragm descends and the longitudinal muscles of the oesophagus contract The descending part of this membrane finds attachment to the stomach Interlaced amongst its fibres are small pads of fat which act as a plug against increased intra abdominal pressure



FIG 73 —This radiograph was taken with the patient erect and in full inspiration The hiatal constriction of the oesophagus is clearly defined There is no infra-diaphragmatic oesophagus

The cardiac sphincter

The existence of a sphincter at the cardia has been debated for years According to anatomical definition there is certainly no true sphincter but there is an intrinsic mechanism which prevents regurgitation of gastric contents Many observers notably Jackson considered the pinch-cock action of the diaphragm to be all important but the radiologist frequently sees a small column of barium remaining in the lower oesophagus unaffected by respiratory contractions of the diaphragm The barium will pass into the stomach as soon as the wave of peristalsis initiated by swallowing allows the sphincter to relax Further evidence of a sphincter may be seen in hiatal hernia of the stomach for some cases do not show free regurgitation even when the cardia lies at the ap x of the pouch The effect of the oblique entry of the oesophagus into the stomach is referred to on page 243

Lendrum (1937) drew attention to a small cuff of fibres derived from the oblique muscle of the stomach which extended up the oesophagus for a centimetre or so He thought this arrangement might exert some control at the cardia Lendrum also found that the nuclei of sympathetic nerve fibres were most numerous in the lower part of the oesophagus Such a preponderance leads one to assume that this segment has a special function which Knight s (1934) experimental work with sympathectomy seemed to substantiate

Some indication of the length of oesophagus participating in the sphincteric mechanism may be found in the radiographs of cardiospasm but it is obviously unwise to base any deductions on such a complex disorder In most cases the stenosis is about 2 centimetres long and lies within the hiatus The affected portion would therefore *appear to be the cardiac antrum*

The phrenic ampulla and cardiac antrum

These structures have not yet been clearly defined *anatomically and for over a* century anatomists have been unable to agree whether one or two pouches exist at the lower end of the oesophagus Until the question is solved it appears expedient to recognize two pouches each having its own method of demonstration *The phrenic ampulla is the temporary dilatation which develops in the oesophagus* immediately above the hiatus when the latter is closed against a bolus descending by peristalsis It can be clearly seen on screening and radiology is essential for its demonstration If the diaphragm is contracted by forced inspiration or the Valsalva experiment whilst barium is swallowed the bolus is held up at the hiatus The descending peristalsis causes the medium to collect at the lower end distending it until the pressure within the dilatation equals that of the peristaltic wave After a momentary pause the contraction ring relaxes and most of the medium flows back up the oesophagus The phrenic ampulla collapses but not always completely A smaller pouch may remain and this is thought by some observers to define the insertion of the phreno oesophageal membrane

The lower pouch or cardiac antrum is a small dilatation which extends about 3 centimetres upwards from the cardia It can be demonstrated in the cadaver by distending the stomach and oesophagus with water If there is no infra diaphrag matic segment of oesophagus then the terminal part must occupy the hiatal canal Thus the cardiac antrum lies in the canal and is usually lined with gastric type of mucosa The antrum is therefore one of the possible sources of confusion in diagnosis of the early hiatal hernia

Movements of the oesophagus

Movements of the oesophagus are difficult to observe with the eye and the present description may require modification when more accurate studies have been made with cine radiography Three types of movement are described by Templeton There is a primary wave initiated by the voluntary act of swallowing which appears to pass down the whole length of the oesophagus with the possible exception of the last 2–3 centimetres When observations are made in the erect position it is evident that the forces of gravity play a considerable part in accelerating the passage of fluids The oesophagus appears to contract *in long*

segments as the medium passes down The relaxation of the sphincter of the cardia may be initiated by the upward pull of larynx as swallowing takes place for in the normal person there is no delay and the barium flows directly into the stomach The inhibition of the cardia is maintained if the act of swallowing is rapidly repeated

In the supine position the rate of movement is much reduced and fluid barium is brought down by a steady descending wave of contraction McLaren (1943) showed by kymography that no relaxation preceded the wave Secondary waves of peristalsis resemble the primary but they are not initiated by voluntary move ment They are usually seen in cases of regurgitation when the reflux of barium reaches the segment above the aortic arch Its arrival appears to stimulate a contraction wave and the medium is speedily returned to the stomach

The tertiary type of peristalsis is described by physiologists as tonus contractions which last from a few seconds to several minutes In addition local rapid con tractions of the circular muscle lasting less then two seconds have been recorded by balloons inserted within the lumen Some evidence of this action may be seen in elderly people immediately following the descent of the bolus The normal linear contraction of the oesophagus is replaced by more vigorous contraction of alternate segments of circular muscle and the outline becomes serrated (Fig 74) In pathological disorders such as cardiospasm irregular contractions of the circular muscle may be a striking feature

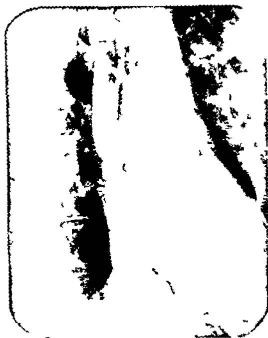


Fig 74 —Early tertiary contractions shown in oesophagus of male aged 70 years This condition was found at barium m al examination and there were no symptoms referable to the oesophagus

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FIG 75—A woman of 50 years who was thought to have angina pectoris but the electro-cardiograph was normal The barium meal showed a classical hiatal hernia of the stomach with free regurgiation In the radiograph the flooded oesophagus shows a posterior indentation just above the aorta which was caused by an abnormal right subclavian artery



FIG 76—Lateral radiograph of the same patient (Fig 75) bending down The hernia is clearly seen The barium has poured through the pouch and passed up the oesophagus A small residue remains in the pouch

Method of examination

For a complete examination of the oesophagus it is wise not to neglect the stomach and the preparation should include starvation for 6 hours previously In this way carcinomas of the gastric fundus presenting clinically as lesions of the oesophagus may not be overlooked The examination should be conducted systematically commencing with a careful fluoroscopic survey of the neck chest and abdomen This is followed by a study of the mechanism of swallowing outlined by barium sulphate preparation of a consistency varying from fluid to semi solid Although it may not be customary to use a barium sandwich conditions are occasionally met with such as spasm which require something solid for their demonstration

The patient is then placed horizontally on the screening table and rotated first into the right and then the left oblique positions In each case the same routine for barium fluoroscopic studies is carried out The removal of the forces of gravity slows the rate of passage down the oesophagus and enables a closer inspection of the contours and movements to be made If thick emulsion is used the medium may remain *in situ* for a considerable time The lower end of the oesophagus can be clearly seen when the patient s right side is elevated When the left side is raised the patient is in the ideal position for demonstrating regurgitation

It is important however to emphasize that regurgitation should occur regularly to be abnormal It is quite common to see at least one reflux during the examination of a normal person There are several methods of demonstrating incompetence of the cardia and a hiatal hernia They are all based on increasing the intra abdominal pressure and the negative pressure within the thorax The simplest technique is to combine deep respiratory movements with firm manual compression of the upper abdomen The maximum force should be exerted just at the end of expiration Such methods will be successful in a high proportion of cases but one may meet with the occasional case in which the release mechanism defies detection It may be that a sudden strain a belch or a swallow allows the hiatus to relax and the sign so vigorously sought for becomes evident with apparently little effort Such an experience emphasizes the uncertainty of the present technique and the need for further research into the control and action of the diaphragm and cardia

The lower end of the oesophagus and gastric fundus may be clearly demonstrated by placing the patient prone and slightly elevating the left side The mucosal pattern is shown by the double contrast of air and barium This position will often enable one to exclude a suspected carcinoma after a filling defect has been observed in the gastric fundus when the patient was erect Such an apparent defect is probably caused by pressure of the left lobe of the liver It is also useful in finding gastric varices which should be looked for in all cases where dilated veins are found in the oesophagus

While screening is the most important part of the examination radiographs should be taken even when the pharynx and oesophagus are normal To obtain a radiograph of the pharynx during swallowing the gloved finger tip should be placed over the laryngeal prominence and the exposure made as soon as it is felt to rise Whenever there is a history of coughing or choking brought on by swallowing which suggests a spill into the trachea or a bronchus barium should

difficult to decide whether or not such a finding represents enlargement of the auricle

The mucosal pattern may be seen after a barium swallow and it consists of 3-4 fine lines parallel to each other When distended by an air bolus the lines disappear as the folds flatten out

Hiatal oesophagus

It is very difficult to visualize the exact anatomical relations of the oesophagus as it passes through the hiatus in the diaphragm It appears to move forwards and slightly to the left and joins the stomach immediately below the hiatus (Fig 73)

Viewed from the front the oesophagus passes through the diaphragm about the level of the eleventh thoracic vertebra and just to the left of the mid line The position of the hiatus can be clearly indicated when a deep inspiration is made or the Valsalva experiment performed The level of the hiatus is seen to be below the cupolas of the diaphragm In the lateral view the oesophagus appears to pass through the diaphragm just behind the centre at a point where the contour is quite convex The oesophagus therefore approaches the hiatus at a slight angle and appears to be more in contact with the anterior than the posterior wall of the tunnel In this segment the radiological mucosal pattern changes from fine to broad coarse lines The change is sometimes quite clearly demarcated and may appear as a ring It is assumed that such an appearance represents the change from oesophageal to gastric mucosa Although this is not an infallible guide it has been proved by the Allison clip method to be correct in a large majority of cases

LESIONS OF THE OESOPHAGUS OF SPECIAL RADIOLOGICAL INTEREST

It was stated in the introduction that the major lesions of the oesophagus are fully described under separate headings To avoid re duplication it is proposed only to mention some points of particular interest to radiologists which may arise in their examination of these cases The number of minor lesions has recently grown and radiologists may claim the principal credit for their recognition Brief descriptions of these abnormalities are given in this chapter

Regurgitation

Free regurgitation of gastric contents into the oesophagus has been observed for many years A large series of cases (105) was described by Robins and Jankelson in 1926 and in 1936 Winklestein drew attention to the oesophagitis associated with regurgitation In spite of these contributions the underlying significance of cardio oesophageal relaxation has not yet been fully appreciated It is a fact that the lower end of the oesophagus does not tolerate constant bathing in pepsin and hydrochloric acid Erosion and peptic ulceration are readily produced which may lead to pain and discomfort behind the sternum to heartburn haematemesis and anaemia In a recent paper Barrett puts forward an attractive suggestion that peptic erosion affects the oesophageal squamous epithelium The penetrating type of ulcer on the other hand is really a gastric ulcer for it develops in the extension of the gastric mucous membrane which may be found in the lower

not be used lest it be inhaled A few cubic centimetres of Lipiodol is the ideal medium for such cases The most useful radiographs of the oesophagus are those taken in the oblique planes and it is important to obtain records of the mucosal pattern as well as the filled oesophagus

Bending position

One of the classical symptoms of reflux peptic oesophagitis is the retrosternal pain or heartburn which is brought on by stooping particularly when it is accompanied by straining It is possible to reconstruct some of the physical changes which occur and observe them fluoroscopically if the patient is placed sideways to the screen and bends down with the knees as straight as possible No better demon stration of the underlying mechanism which causes these symptoms can be made for on straining or deep respiration the gastric hernia is seen to bulge into the thorax Barium pours into the pouch and thence into the oesophagus as freely as if it were being poured through a spout (Figs 75 and 76)

NORMAL RADIOGRAPHIC APPEARANCES

Laryngo pharynx and upper oesophagus

For a number of years in Great Britain it was taught that the epiglottis remained upright during swallowing and negative pressure played a large part in drawing the bolus into the oesophagus Now it is generally accepted that the epiglottis does turn over the larnygeal aditus during swallowing and this is clearly seen in many elderly people in whom the epiglottis moves slowly In the lateral plane the column of barium should be quite regular but indentations on the posterior wall may be caused by osteophytes More rarely a rounded shelf like defect appears which is considered to be produced by the crico pharyngeus muscle On the anterior wall behind the lower margin of the cricoid cartilage a small linear defect may become apparent during swallowing This can be confused with the post cricoid web Viewed from the front the column appears wide as it descends through the pyriform fossae and narrows a little as it passes through the upper oesophageal sphincter

Thoracic oesophagus

The close contact of the oesophagus with the aorta and pericardium is the reason for using the barium filled oesophagus in the study of the heart These structures cause several impressions on the oesophagus which are easily recognized The aorta as it turns over to the descending position indents the left anterior aspect of the oesophagus This indentation enables the observer to estimate quite accurately the diameter of the aorta Immediately below it the oesophagus lies behind the left bronchus and the right pulmonary artery Under normal conditions the impression caused by these structures is negligible Sometimes when the patient is supine the indentation produced by the left bronchus causes a marked linear filling defect running obliquely across the barium column The oesophagus next lies posterior to the left auricle which in the normal adult makes no impression on the barium column In children and young adults however there is often a slight bulge into the anterior oesophageal wall and it becomes very

responsible for all cases of regurgitation Much has also to be learned about the voluntary control of the diaphragm and the mechanism of belching and swallowing Examples of such phenomena are illustrated in the following cases A young man aged 18 years could voluntarily bring back food into his mouth by a manoeuvre which appeared to be a combination of belching and vigorous contraction of the abdominal muscles He did *in fact* cause the fundus of the stomach and cardia to herniate into the thorax and the gastric contents flooded back into his mouth The main point of interest lay in his ability to prevent this herniation when the usual technique was applied and it was only possible to radiograph the hernia when his full co operation was obtained This remarkable feature indicates that voluntary control of the diaphragm might be a factor in the production of hernias which appear only intermittently (Figs 78 and 79)

In another case a woman aged 38 years there was a history of dyspepsia for over 20 years During the past 4 years she complained of intermittent attacks of a sharp pain under the right costal margin a cholecystogram proved to be normal the barium meal appeared to be normal but after heavy compression a small hiatal hernia was found Regurgitation was observed although it was not easily produced When the patient was lying supine with the left side raised and asked to swallow it was noted that *on each occasion a small reflux occurred into the* lower oesophagus and a combination of deglutition and compression greatly increased the amount and frequency of the regurgitations (Figs 80 and 81)

A third example demonstrates the effect of belching in cases where the hiatus *is not quite normal* A woman aged 59 *years complained of flatulence discomfort* and upper abdominal pain for many years The barium meal revealed at first no abnormality and there was no reflux with the routine compression After belching a small hernia of stomach appeared through the hiatus and regurgitation occurred regularly While compression was exerted the hernia remained present (Fig 82)

Robins and Jankelson *(1926) considered* some of their cases of cardio-oesophageal relaxation were improved with physostigmine and atropine made the condition worse The effect of drugs in such cases seems to have been ignored and should provide a useful line of research

Bearing *in mind however the very close relationship between* regurgitation and herniation it is not difficult to realize that the former almost becomes a pre requisite in the diagnosis of the latter The main exception to this rule is found in some of the para oesophageal types of hernia wherein the oesphagus enters the pouch at a lower level often at or close to the hiatus and the valvular mechanism is still preserved

The recognition of a large hiatal hernia presents no difficulty but the early cases may be most confusing for it is by no means easy to distinguish between the phrenic ampulla and a small gastric pouch If one also believes that the cardiac antrum of the oesophagus *lined* with gastric mucosa may protrude or appear to protrude through the hiatus then the problem becomes even more perplexing There is in almost every case one distinguishing feature of herniation and that is the ease with which barium from the stomach can regurgitate into the oesophagus particularly when aided by certain technical manoeuvres True regurgitation however must be distinguished from the reflux up the oesophagus which follows the relaxation of the contraction ring at the apex of the phrenic ampulla

oesophagus In more advanced cases there is a spastic contraction of the lower oesophagus which causes obstructive symptoms These may become severe and intractable especially when the spasm is superseded by fibrosis Perforation and neoplastic changes are also described Such are the effects of regurgitation

As greater attention has been paid by radiologists to the lower end of the oesophagus and cardia the diagnosis of hiatal hernia of the stomach has been made much more frequently and it has become obvious that the sliding type of hernia with a short oesophagus is almost invariably associated with incompetency of the cardia and free regurgitation No satisfactory explanation for this break down in the physiological protection of the oesophagus has yet been put forward



FIG 77—Lateral view of lower oesophagus in the bending position showing flooding which occurred on straining No hernia found

but many observers agree with Jackson that the diaphragm is the chief bulwark against regurgitation No radiologist will doubt however that there is a sphincteric action at the lower end of the oesophagus but its efficiency depends largely upon the direction of entry of the oesophagus into the stomach As Dick and Hurst (1942) pointed out the oblique entry into the lesser curvature allows a valve like mechanism to operate whereas in the sliding hernia the oesophagus enters the stomach at the apex of the pouch and the valve ceases to exist

It has become apparent however that factors other than herniation may affect the competency of the cardia At times the oesophagus may be uniformly large the cardia appears widened and yet no hernia of the stomach is evident (Fig 77) In such cases it is possible that the primary defect may lie in the hiatus or in the cardia It is therefore important to bear in mind that gastric herniation is not

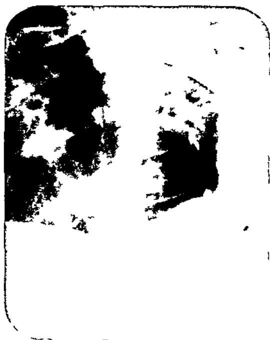


FIG 80 —Skiagram of woman of 38 years taken in the supine left oblique showing the lower oesophagus empty No hernia or regurgitation could be demonstrated by routine methods



FIG 81 —Same case as FIG 80 The radiograph shows a slight flooding of the lower oesophagus which occurred immediately after swallowing



FIG 78—Lateral bending film of young man with voluntary control of hernia Radiograph taken before the hernia was produced



FIG 79—Shows a moderately large gastric hernia filled with some barium and secretion Silver clips are present One has been attached to the mucosal junction at the cardia a second clip lies in the gastric pouch



FIG 83 —A woman of 33 years complained of severe retrosternal pain brought on particularly by swallowing food Heartburn had been severe during the later stages of pregnancy but the acute pain started after delivery Skiagram taken 5 months later shows irregular narrowing of the lower half of the oesophagus



FIG 84 —Same case as Fig 83 Radiograph taken 3 months later showing almost complete stenosis with dilatation above Most of the lower oesophagus has contracted dragging with it a small pouch of stomach

The association of pregnancy and regurgitation

It is natural to suppose that pregnancy will impose considerable strain on the hiatus and the liability to herniation must increase It can reasonably be assumed that much of the heartburn suffered in the later stages of pregnancy is related to relaxation of the cardia and regurgitation Some observers comment on the frequency with which hiatal hernias are found in the last three months of pregnancy Thus it appears logical to expect a preponderance of parous women to be affected by herniation In the early series of Allison s cases this hypothesis was not sustained for the hernias were found almost equally in both sexes Harrington s figures (1943) show that men are affected twice as often as women As an explanation of the smaller incidence in women it is suggested that the laxity of the abdominal wall in parous women prevents a great increase in the intra abdominal pressure



FIG 82—Radiograph of woman of 59 years who had no hiatal hernia on routine examination but after belching the hernia appeared and regurgitation occurred

One of the worst cases of peptic ulceration of the oesophagus personally observed developed in the early stages of pregnancy while the patient was suffering from severe hyperemesis The association of vomiting and the development of peptic ulceration has been noted on several occasions and indeed it seemed that in pregnant women vomiting was a more important factor than the increasing intra abdominal pressure In another severe case the ulcer developed a few days after delivery and like the first required radical surgical treatment (Figs 83 and 84)

Rumination

True rumination might be described as the capacity to bring back at will into the mouth food which has been previously swallowed Ruminators of this type are



FIG 83 —A woman of 33 years complained of severe retrosternal pain brought on particularly by swallowing food Heartburn had been severe during the later stages of pregnancy but the acute pain started after delivery Skiagram taken 5 months later shows irregular narrowing of the lower half of the oesophagus



FIG 84 —Same case as Fig 83 Radiograph taken 3 months later showing almost complete stenosis with dilatation above Most of the lower oesophagus has contracted dragging with it a small pouch of stomach

very rare but two cases which were examined recently showed features of interest The first an elderly woman volunteered the history that when a child she could swallow a sweet and then reproduce it in her mouth a short time later This accomplishment she had often found useful in church and school Radiological investigation showed a large hiatal hernia of the stomach a patulous cardia and wide short oesophagus The method of returning the gastric contents seemed to be akin to belching (Fig 85)

The second case was in a young man who displayed an extraordinary degree of voluntary control of his hernia He was referred to on page 253



FIG 85 —Radiograph of ruminator showing hiatal hernia and dilated oesophagus which although shortened shows slight redundancy as the hernia increases in size

Congenital stricture and shortening of the oesophagus

A great deal has been written about various lesions associated with stricture and shortening of the oesophagus In most of these cases the strictures were found about the level of the seventh thoracic vertebra Below the narrowing the lumen widened out and was identified as a partial thoracic stomach While developmental defects can explain these abnormalities it has been shown recently that in the majority of cases the stricture and shortening of the oesophagus followed peptic oesophagitis and are therefore acquired lesions The constant regurgitation of gastric juices however may be due to congenital defects either at the cardia or at the hiatus which render ineffective the physiological barrier

Clinically these cases present with oesophageal regurgitation which often may be blood stained The regurgitation always becomes more noticeable after weaning but there is some inconstancy about its appearance for it may not occur with every feed Regurgitation may be most pronounced at the beginning of a meal after which the rest is swallowed readily alternatively it may occur at the end of a meal To find an explanation for such variations one falls back on spasm provoked by certain foods or perhaps by psychogenic factors The oesophageal contraction following vagal stimulation which has been found experimentally lends some support to such a hypothesis

Occasionally one may find a simple spasm also intermittent in appearance and variable in degree which may result from an active tuberculous infection in an adjacent lymphatic gland It is this type of lesion which is overlooked radiologically unless bulky food is added to the opaque medium

Regurgitation at this age is by no means confined to oesophageal obstruction but may arise from the stomach Posseting in a well fed baby is regarded as a natural phenomenon The radiological studies made of the lower end of the oesophagus have brought out the difficulties of defining the phrenic ampulla and a small protrusion of the stomach through the hiatus Paterson (1919) and Brown Kelly (1919) first drew attention to a sliding hiatal hernia of the stomach which they considered to be a normal condition in infants There is no doubt that regurgitation may occur when a baby s stomach is fully distended but in the normal case it is intermittent and cannot be readily produced The baby may be held upside down and still the oesophagus is protected by the diaphragm and cardia When there is some abnormality however which interferes with the defence mechanism then regurgitation takes place constantly with or without physical aids Cases are not infrequently seen in which the oesophagus appears to be of normal length but is wide and hypotonic (Fig 86) The cardia is relaxed and the stomach seems to lie below the diaphragm Sudden changes of pressure which occur for example at the end of a prolonged expiratory howl when there is a sharp rise in the negative intrathoracic pressure tend to dilate the oesophagus and flood it with gastric contents

It has already been stated that congenital short oesophagus is rare but there may be other congenital lesions which permit this physiological break down If the crura or the dome of the central tendon of the diaphragm or the phreno oesophageal membrane are imperfectly developed the stomach will herniate into the thorax In all these cases reflux oesophagitis will occur and the oesophagus may become shortened and narrow The recognition of these abnormalities is most important for all too often it is found that by the time the cases are examined the contraction of the oesophagus has become permanent and round-celled infiltration of the walls with peptic ulceration has taken place The surgical treatment is formidable and carries considerable risks On the other hand medical treatment may be adequate in early cases if means are taken to reduce regurgitation It appears that if satisfactory control is maintained then as growth takes place regurgitation becomes less pronounced and finally cured

True congenital stenosis which is found close to the bifurcation of the trachea is rare



FIG 86—A radiograph of a baby of 4 months with frequent regurgitation The barium meal shows a patulous cardia and a wide hypotonic oesophagus but no definite gastric hernia



FIG 87—Abnormal tertiary contractions with pseudo diverticula formation in elderly man with intermittent attacks of dysphagia The large lower pouch was found to be a gastric hernia

Abnormal muscular contractions

In the description of normal peristalsis it was mentioned that occasionally the oesophagus presents a serrated margin after the passage of barium This change occurs in elderly people and is thought to be due to muscular imbalance in which there is over action of segments of circular muscle In a mild form the condition does not give rise to symptoms (Fig 74)

There is a rare abnormality which appears to be an advanced stage of this mild disorder It has various synonyms such as curling corkscrew or ripple oesophagus and tertiary contractions with functional diverticula Those most often affected are elderly men It was thought that the condition was a Parkinsonian phenomenon but this has not yet been proved Other suggestions were adhesions or contractions of the small slips of tissues which pass between the oesophagus and its mediastinal structures

There seems to be a loss of co ordination between the circular and longitudinal muscle which becomes evident on swallowing Instead of permitting the normal rapid descent of the opaque medium the lower half of the oesophagus goes into a state of frenzied excitation wherein narrow ring like contractions occur and the oesophagus distends between them so that it resembles a chain of bubbles These contractions may disappear and reappear with great rapidity until the oesophagus is empty The contraction rings and distended sacs are very constant in position and permanent diverticula may ultimately form In several cases a large pouch has been noted immediately above the diaphragm which on further examination was found to be stomach (Fig 87) Such a finding favours the hypothesis of a muscular disorder for excessive longitudinal contractions would drag up the stomach The irregular movements however do not necessarily appear as the bolus is swallowed but become evident immediately after the bolus has passed

Recently Scheinmel and others (1949) studied the effects of drugs on this condition and reported that after the administration of nitrites the irregularities dis appeared Other varieties of irregular oesophageal contractions have recently been attracting attention When screening patients suffering from retrosternal pain and suspected of having angina pectoris it is occasionally noted that the heart appears normal but the oesophagus shows irregular contractions as barium is swallowed

One such example is seen in Fig 88 This patient suffered very severe pain particularly at night and relief was obtained only by opiates On oesophagoscopy nothing abnormal was found but on several radiological examinations lasting over a period of 4 years the same irregular contraction of the lower oesophagus was noted After the main bolus had passed the oesophagus contracted irregularly at two points about 3 centimetres apart and the intervening segment became dilated Octyl nitrite had no action on these contractions

Another patient who complained of severe retrosternal pain showed more extensive irregular contractions (Fig 89) On the other hand such changes in the oesophagus may be found in patients who are symptom free

Sclerodermia

Dysphagia has been recorded sufficiently often in patients suffering from sclerodermia to suggest that the disease shows a predilection for the oesophagus Indeed sclerodermatous changes in the lowest segment of the oesophagus have been



FIG 88—Irregular spasm with local dilatation in the mid oesophagus in a woman of 40 years who complained of severe retrosternal pain



FIG 89—Irregular spasm in the lower half of the oesophagus found in a male of 46 years who complained of severe retrosternal pain especially after swallowing

described in a small number of cases which have come to autopsy Radiological examination has shown certain changes which some authors are inclined to describe as typical of the condition In a group of cases published by Olsen and others (1945 1948) it was suggested that when acrocyanosis accompanied sclero dermia there was a high incidence of dysphagia The dysphagia however does not necessarily result from changes in the lower oesophagus and a careful examination of the upper end and pharynx must not be omitted The muscles of deglutition may become affected and the result is similar to bulbar palsy in which the dysphagia is due to the inability of the muscles to perform their normal function

It is however at the lower end of the oesophagus where the most interesting changes occur Although dysphagia is present in most of the cases showing these changes a few patients are symptom free The earliest radiological signs are related to interference with effective peristalsis so that an opaque bolus appears to pass down the oesophagus with less than normal speed Muscular contraction is not so vigorous and the retention of a bolus in the oesophagus does not stimulate adequate secondary peristalsis A slight stenosis probably a centimetre in length may be observed some 2-3 centimetres above the diaphragm at or close to the site of the phrenic ampulla As the condition advances the narrowing becomes more pronounced and the obstruction greater causing the oesophagus above to dilate Below the narrowing the lumen of the oesophagus appears wider than normal and the mucosa is similar to that of the stomach The appearance is now identical with many cases of peptic ulceration of the oesophagus and hiatal hernia of the stomach Considering these observations it seems reasonable to suppose that the sclerodermatous process affects the competence of the cardia with the result that the gastric juices freely regurgitate excoriating the oesophageal mucosa and setting up peptic oesophagitis Thus the gross radiological changes are due to a secondary effect of the disease

This explanation however is not supported by observations made in two cases recently observed The first case a male aged 40 years with the classical facies and extremities had only a slight degree of narrowing of the oesophagus (Fig 90) and yet in spite of the usual manipulations while screening no regurgitation from the stomach was observed The second case a classical picture of peptic ulceration stenosis and short oesophagus came to autopsy and no stenosis could be found (Fig 91) Evidence of clerodermia was said to be present in the submucosa but it must be admitted that such changes bear a strong resemblance to the round celled infiltration seen in peptic oesophagitis No satisfactory explanation of the stenosis can be offered unless it is due to severe spasm involving circular and longitudinal muscles possibly of vagal origin

A third case is described to illustrate the possibility of coincidence It is not without importance to emphasize that this case was diagnosed as one of dermato myositis and not sclerodermia although many authorities consider the two con ditions as different manifestations of the same process This patient almost helpless from muscular infiltration and unable to sit up complained of dysphagia which she clearly stated was a feeling of obstruction in the root of the neck On fluoroscopy the mechanism of swallowing was defective for it appeared that there was insufficient propulsive force to push the whole bolus into the upper oesophagus



FIG 90 —A male of 40 years suffering from scleroderma with calcinosis complained of a little dysphagia A slight constriction of the lower end of the oesophagus situated proximal to the hiatus was found Slight irregularity of the mucosa and some thickening of the wall was noted Muscular movements of the oesophagus were reduced but there was no delay in emptying when the patient was erect

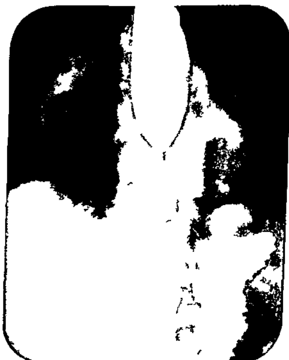


FIG 91 —A woman of 35 years with gross sclerodermatous changes complained of marked dysphagia A constriction of the oesophagus was found a little above the hiatus Below it was a small pouch and it *was considered to be typical of* peptic ulceration with stenosis and hiatal hernia At autopsy no stenosis was found



FIG 92—Demonstrates the barium flooding back into the posterior nares after attempting to swallow



FIG 93—Shows narrowing of the lower oesophagus with a small gastric pouch above the hiatus and free regurgitation of barium Vigorous muscular movement returned the barium to the stomach A small pulsion diverticulum is apparent posterior to the pulmonary artery



FIG 94 (*a* and *b*) —Radiographs showing a lobulated and oval filling defect with smooth mucosa and ring sign Soft tissue shadow of similar length is present Diagnosis of simple tumour was made but the condition was found to be tuberculous adenitis

(*a*)



(*b*)

The barium which remained in the pharynx passed back into the posterior nares much to her discomfort (Fig 92) Part of the bolus entered the oesophagus and the primary waves of peristalsis appeared to be quite efficient After reaching the stomach a slight amount of abdominal compression showed that reflux into the oesophagus readily took place and a hiatal hernia of the stomach was demonstrated The flooding of the oesophagus stimulated secondary peristalsis which was quite normal This case illustrated the possibility of coincidence for although it seemed probable that the dermatomyositis was responsible for the initial dysphagia a classical hiatal hernia with oesophagitis was displayed at the lower end (Fig 93)

Oesophageal fistula

A fistula between oesophagus and trachea or main bronchus is so often due to malignant disease that the complication is viewed with considerable despondency It is not so widely known that in a number of cases of lung abscess or bronchiectasis which have failed to respond to orthodox treatment the primary source of infection is a fistula of this nature Whether the fistula is of congenital origin or acquired such as may follow a breaking down tuberculous adenitis is difficult to determine and is of no significance Fistula may form in other directions involving the pericardium the mediastinum and the pleura Occasionally the prolonged use of a drainage tube in a chronic empyema cavity may result in necrosis of the oesophagus and the formation of a fistula

Although it would appear easy to demonstrate such a fistula by observing the leakage of Lipiodol during swallowing it is often very difficult to define the track The medium descending down the oesophagus may travel so quickly that it fails to enter the fistula The routine examination is completed in the supine position and it is obvious that if the fistula affects the anterior oesophageal wall which is the common site it will not be outlined

When these fistulae are suspected the greatest technical care in the radiological examination is required In addition to the routine positions the patient is examined prone and rolled slowly from side to side while small sips of Lipiodol are swallowed In this way the chances of some opaque medium finding its way into a bronchus are greatly increased The fistula can then be radiographed in different positions and accurately localized

Simple tumours of the oesophagus

Simple tumours of the oesophagus are very rare but the satisfaction of making the correct diagnosis and the high prospect of a surgical cure justify their inclusion in this chapter Most of the tumours prove to be leiomyomas but others including fibromas and lipomas have been described Their intramural growth brings about an interesting series of radiological changes

The striking radiological feature is a filling-defect in the lumen of the oesophagus The defect may be round or oval and sometimes the stream of barium may be deflected or forked as it passes over the mass The mucosa is smooth and appears stretched over the tumour The normal longitudinal folds disappear over the convexity of the defect but reappear at the upper and lower margins After swallowing barium an arc like shadow may be found at the lower border of the defect The explanation of this feature is that a thin layer of barium collects in

the groove which develops between the lower margin of the tumour and the unaffected oesophageal wall Such a shadow which is very characteristic indicates that the mass sags a little as it projects into the lumen causing the mucosa to become infolded

A suitable radiograph will outline the soft tissue opacity projecting from the oesophageal wall and the long diameter of this mass should equal the length of the filling defect if the tumour is intramural This finding can be contrasted with an oesophageal defect produced by aneurysm or enlarged glands for in the latter cases the mass is greater in length than the defect

Like other lesions they produce symptoms painful or obstructive often of a duration so long that cancer seems improbable In size there is considerable variation In one case the defect resembled that of an aberrant right subclavian



FIG 95 —Gross gastric and oesophageal varices found in a long standing case of splenic anaemia The arrows indicate one large gastric varix running into the oesophagus

artery and indeed it was diagnosed as such in preference to a simple tumour Another presented as mega oesophagus of enormous dimensions with a large smooth filling defect lying behind the heart and immediately above the diaphragm The most confusing appearances were brought about by a leiomyoma which appeared to arise at the cardia involving both stomach and oesophagus but projecting above the diaphragm

Another cause of erroneous diagnosis is tuberculous adenitis A woman aged 23 years complained of slight dysphagia first with solids then also with fluids This was described as a retrosternal pain brought on by swallowing It was not severe and did not last more than a few days She was examined radiologically before the symptoms subsided and a lobulated mass causing a slight but

persistent filling defect in the mid oesophagus was found The mucosa was intact but a typical ring shadow was produced The oesophagoscopy did not materially assist except to confirm the intact mucosa The radiological examination was repeated and the defect was found constant At operation a large caseating tuberculous gland was found in the carina firmly adherent to the left bronchus oesophagus and pericardium A number of smaller affected glands were lying adjacent The wall of the oesophagus was invaded and during separation pus escaped It is obvious that this condition may lead to the formation of a sinus and diverticulum or a bronchial or pericardial fistula

Thus tuberculous adenitis may produce all the radiological signs of an intra mural o sophageal tumour The main distinguishing feature was the length of history In my experience of simple tumours the history of dysphagia extends over a long period even several years (Fig 94 (*a*) and (*b*))

Varices

Oesophageal varices are responsible for some of the most severe and fatal attacks of haematemesis It is important to remember that they occur at any age and not infrequently in young children Varices should always be carefully sought for in all cases of symptomless haematemesis especially if there is any evidence of splenomegaly The radiological diagnosis in advanced cases presents no difficulty but in the early stages varices are easily missed

Oesophageal varices however are always accompanied by varices of the short gastric veins These cross the fundus of the stomach in a worm like fashion running towards the cardia through which some may pass It may however be difficult to distinguish them from mucosal folds Sometim s these gastric varicosities are more easily seen than the dilated oesophageal veins and they should always be sought for at or about the cardia in both supine and prone positions The latter is especially good for a double contrast is obtained with the fundal air bubble (Fig 95)

In cases of haematemesis there is usually a superficial peptic ulcer eroding a superficial varix and it is extremely unlikely that the bleeding point can be identified radiologically Frequently the gastric veins are affected and large clots may add to the difficulties of examination

Carcinoma of the oesophagus

Although this lesion is dealt with elsewhere it seems justifiable to add a short note of radiological interest

In spite of the innumerable examinations of the oesophagus the accidental discovery of a malignant growth is virtually unknown It would appear that either the radiologist is unable to detect cancer until it produces symptoms by which time certain clinical signs must be evident or our present method of examination is too crude The truth probably lies in that an exhaustive and detailed examination is not practicable in the large majority of cases Attention however must be drawn to one common error Radiologists frequently assume that a short smooth stricture at the lower end of a dilated oesophagus is cardiospasm Carcinoma of the fundus of the stomach may grow very silently until it invades the lower oesophagus Although the first spread may be submucosal which adds to the diagnostic

difficulties the effect is one of obstruction Until the growth ulcerates or becomes advanced the lining of the stenosis may appear quite smooth and a radiograph of a barium filled oesophagus may be indistinguishable from cardiospasm The radiological differentiation is based on a careful observation of the peristaltic movements In organic obstruction due to growth impaction or simple stenosis the primary or secondary waves of peristalsis may be exaggerated and the barium appears to be squeezed up and down in a vigorous manner These movements must not be confused with the appearance of disordered secondary and tertiary contractions with the rippling margins so often seen in cardiospasm Moreover air is rarely seen in the gastric fundus in cardiospasm but it is almost always present in cancer and outlines the mucosal irregularity or mass of growth even without the aid of barium It becomes apparent that no diagnosis of cardiospasm *should be made until the stomach is found normal*

In recent years when a number of oesophageal strictures have been recognized as a sequel to chronic peptic ulceration much speculation has arisen regarding those cases hitherto diagnosed erroneously as cancer As described elsewhere the finding of a pouch of stomach immediately below the stricture protruding through the oesophageal hiatus strongly favours the diagnosis of peptic ulceration Any suggestion of a filling defect or irregular ulceration should be carefully investigated for an increasing number of cancers of the oesophagus complicated by hiatal hernia or alternatively cancer of the fundus arising in the gastric hernia have been described

The majority of cases fall into the latter group and various authors (Smithers 1945) have endeavoured to find explanations for the combined lesions Three suggestions are favoured—coincidence chronic irritation by the regurgitation of gastric juices and lastly that malignant disease brings about a vagal stimulation resulting in contraction of the lower oesophagus thus the hernia develops secondarily to the neoplasm The latter explanation is favoured by Smithers but *it is probable that coincidence will prove to be the final answer* for the diagnosis of hiatal hernia is increasing so rapidly that it will soon be regarded as a common lesion

REFERENCES

Abowitz J (1945) *Amer J Roentgenol* 54 483
Allison P R (1948) *Thorax* 3 20
— Johnstone A S and Royce G B (1943) *J Thorac Surg* 12 432
Alvarez W C (1939) *An Introduction to Gastro Enterology* London Heinemann
Barclay A E (1930) *Brit J Radiol* 3 534
— (1933) *The Digestive Tract* London Cambridge University Press
Barrett N R (1950) *Brit J Surg* 38 175
Berk M (1945) *Gastroenterology* 5 290
Bersack S R (1944) *Radiology* 42 220
Bourne W A (1949) *Lancet* 1 392
Briggs P J Dick R C S and Hurst A F (1939) *Proc R Soc Med* 32 1473
Brown Kelly A (1919) *J Laryng* 34 289
Caffey J (1945) *Pediatric X ray Diagnosis* Chicago Year Book Publishers
Clerf L H and Manges W F (1933) *Ann Otol etc St Louis* 42 1058
Dick R C S and Hurst A (1942) *Quart J Med* 11 105
Feldman M (1938) *Clinical Roentgenology of the Digestive Tract* Baltimore Wood

REFERENCES

Findlay L (1933) *Thomson s Clinical Study and Treatment of Sick Children* London Oliver and Boyd
— and Kelly A B (1931) *J La yng* 46 797
Hale Clayton H and Schatzki R (1944) *Amer J Roentgenol* 51 407
Harper R A K and Tiscenco E (1945) *Brit J Radiol* 18 99 208
Harrington S W (1943) *Amer J Roentgenol* 49 2 185
Hawes L E (1944) *Amer J Roentgenol* 51 575
Holmgren B S (1944) *Acta Radi l* 25 40
Johnstone A S (194?) *J Anat* 77 97
— (1943) *Brit J Radiol* 16 192 357
Kenworthy R A and Welch C A (1948) *Surgery* 23 745
Knight G C (1934) *Brit J Surg* 22 864
Lendrum F C (1937) *Arch Intern Med* 59 474
McLaren J W (1943) *Brit J Ra li l* 16 270
Melamed A and Zimmerman B M (1946) *Amer J Roent enol* 55 20
Mosher H P and McGregor G W (19?8) *Ann Otol etc St Lou is* 37 1?
Olsen A M O Leary R A and Kirklin B R (1945) *Arch Intern Med* 76 189
— and Harrington S W (1948) *J Thorac Surg* 17 189
Paterson D R (1919) *J Laryng* 34 289
Robins S A and Jankelson I R (1926) *J Am r med Assoc* 87 1961
Schatzki R (1940) *Arch Surg* 41 1084
— and Hawes L E (194?) *Amer J Roentgenol* 48 1
Scheinmel A Priviteri C A and Poppel M H (1949) *Ibid* 62 807
Schwarz G S and Skinses O K (1949) *Ibid* 62 359
Smithers D W (1945) *B it J Ra liol* 18 199
Steiner G (1946) *Ibid* 19 2 0
Templeton F E (1944) *X ray Examination of the Stomach* Chicago University Press
Vinson P P (192?) *Minn Med* 5 107
Winklestein A (1936) *J Amer m d Assoc* 104 905
Wyllie W G and Field C E (1946) *Arch Dis Child* 21 218

CHAPTER 12

GASTRIC SECRETION

SECTION I

MECHANISM

R F DAVIES

THE NATURE AND SITE OF FORMATION OF OXYNTIC CELL SECRETION

THE stomach can elaborate a secretion in which the hydrogen ions are about 4 000 000 times more concentrated than in blood This remarkable fact has attracted much research and speculation on the nature of the processes involved but despite more than 100 years of effort many details are still uncertain Prout in 1824 first showed that the stomach forms hydrochloric acid and since then nearly 40 hypotheses regarding the mechanism have been put forward These have been reviewed recently (Davies 1951) and most of them shown to be either incomplete or untenable The formation of gastric hydrochloric acid requires a continuous expenditure of energy and this fact rules out any mechanism of the process depending solely on selectively permeable membranes The existence of a sieve allowing a one way passage of hydrogen and chloride ions and thereby forming gastric hydrochloric acid would be a violation of the second law of thermodynamics and may therefore be regarded as impossible

Gastric juice is a mixture of the secretions from many types of cells which between them produce hydrochloric acid sodium and potassium chloride and bicarbonate mucin pepsin and various minor constituents Little is known about the formation and secretion of the organic constituents but the primary inorganic secretions are normally produced in concentrations approximately isotonic with the blood (Hollander 1943 Babkin 1950 Fisher and Hunt 1950)

Although it has been generally accepted that the oxyntic (or parietal) cells form the hydrochloric acid there has been controversy for nearly 100 years concerning the site of formation of the acid Bernard (1858) believed that a precursor was secreted which turned into hydrochloric acid in the stomach and this possibility has been abandoned only in the last few years It is now known that the intracellular canaliculi of the oxyntic cells are strongly acid during secretion (Fig 100) (Bradford and Davies 1950) and that the primary juice is a simple inorganic solution In man its composition is about 160 millimolar hydrogen ions 10 millimolar potassium ions and 170 millimolar chloride ions (Fisher and Hunt 1950)

THE BIOCHEMICAL APPROACH TO THE STUDY OF GASTRIC SECRETION

The classical methods of physiology have thrown light on many of the inter relations between the stomach and the rest of the body but our knowledge of

the mechanism of acid secretion is quite recent and has largely resulted from a biochemical approach and investigations on tissues isolated from the body With such isolated tissues it is possible to control the conditions and make precise measurements of acid secretion and metabolism and thus obtain a much deeper insight into the detailed mechanisms than is possible with the intact organism

Delrue (1930) first showed that acid secretion could be studied *in vitro* with a sheet of isolated frog gastric mucosa which separated two glass chambers The submucosal side of the membrane was bathed in a buffered physiological saline solution and the glandular side secreted hydrochloric acid into water or an isotonic sodium chloride solution Histamine was found to stimulate acid secretion under these conditions Isolated gastric mucosa from frogs and toads has been used extensively since then because the mucosa is so thin that sufficient oxygen can easily diffuse into it from the medium Most mammalian gastric mucosae are far too thick for such experiments but it has been found that isolated mouse stomachs can be used successfully in saline solutions if placed in small bombs at a pressure of about four atmospheres of oxygen (Davenport and Chavre 1950)

Experiments on sheets of gastric mucosa—In early attempts to investigate the metabolism of acid secreting gastric mucosa pieces of this membrane were incubated in Warburg microrespirometers in a physiological saline solution containing sodium bicarbonate Any new formation of hydrochloric acid in the system as a whole would then cause a liberation of carbon dioxide from the medium which should be observed by changes of the manometer readings However these were complete failures as no trace of acid secretion was ever detected even though the rate of respiration of the isolated tissue was increased by histamine

There were two possible explanations either the gastric mucosa was not secreting hydrochloric acid or it was also forming exactly as much alkali as acid so that the carbon dioxide liberated by the acid would just balance the carbon dioxide needed to neutralize the alkali In order to investigate this a method was needed to separate the secretions from the saline medium

Experiments on tied tubes of gastric mucosa—It was found that the serosa and muscle layers could be dissected from the stomach of the frog or toad to leave an intact tube of the gastric mucosa This was washed emptied and tied with fine silk at both ends to form a water tight bag weighing usually 100–200 milligrams (Figs 96 and 97) When such a tied tube of mucosa was incubated in a Warburg cup containing the nutrient saline medium in an atmosphere containing oxygen it filled up with secretions within a few hours when stimulated with histamine (Fig 98) At the end of the incubation the contents were removed and found to contain hydrochloric acid together with some mucus (Davies 1948)

Production of hydrochloric acid and bicarbonate ions by tied tubes of gastric mucosa—Early experiments showed that when acid secretion commenced it was accompanied by a large overall uptake of gas when the tissue was incubated in a bicarbonate-containing saline gassed with 5 per cent carbon dioxide and 95 per cent oxygen Quantitative estimations were made of the hydrochloric acid present in the secretion the small amount of lactic acid formed in the medium and the changes in the concentration of sodium bicarbonate The results of a typical experiment are shown in Table I



FIG 96

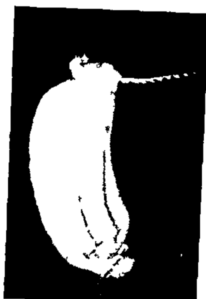


FIG 97



FIG 98



FIG 99



FIG 100



FIG 101

TABLE I

PRODUCTION OF ACID AND BICARBONATE AND UPTAKE OF CARBON DIOXIDE BY A TIED TUBE OF FROG GASTRIC MUCOSA

(17 6 milligrams dry weight mucosa produced 86 milligrams secretion 25° C 5½ hour incubation Medium frog saline gassed with 5 per cent carbon dioxide in oxygen 5 × 10^{-5} molar histamine) Note 22 4 × 10^{6} microlitres = 1 gram molecular weight

	Estimated error (microlitres)
Hydrochloric acid in secretion - - - -	+ 183 (± [illegible])
Change in bicarbonate content of nutrient medium	+ 154 (± 6)
Change in lactate content of nutrient medium -	+ 38 (± 4)
Change in bicarbonate corrected for lactic acid -	+ 19[illegible] (± 10)
Carbon dioxide absorbed by the mucosa - -	+ 180 (± 2)

After a correction had been made for the lactic acid production it was found that the amount of acid secreted was equal to the amount of carbon dioxide absorbed and to the increase in the bicarbonate content of the nutrient medium The overall experimental error in these direct estimations was about 5 per cent but the demonstration that acid was actually being secreted by the tissue combined with the lack of an extra carbon dioxide output during similar experiments with open sheets of mucosa shows that the stomach produces exactly as much alkali as acid The neutralization of this alkali by carbon dioxide is probably complex and involves the cytoplasmic buffers (Crane Davies and Longmuir 1948)

It is surprising that whilst acid is being secreted into the lumen of the stomach an exactly equivalent amount of bicarbonate passes into the blood However it has long been known qualitatively that there is an increase in the base content of the blood during acid secretion It is this increased alkalinity of the blood that leads to the appearance of the alkaline tide in urine following meals This was first described by Bence Jones (1845)

Respiration and acid secretion of gastric mucosa —Oxyntic cells comprise only $\frac{1}{10}$ of the volume and $\frac{1}{20}$ of the dry weight of the gastric mucosa (Davies 1951 Engstrom and Glick 1950) therefore only a small but unknown fraction of the basal respiration of this tissue can be assigned to these cells The rate of

FIG 96 —Excised frog stomach muscles intact and contracted 3 0

FIG 97 —Isolated frog gastric mucosa tied with fine silk thread at both ends × 3 0

FIG 98 —Normal distended tied bag of frog gastric mucosa after 5 hours stimulation with histamine in bicarbonate saline gassed with 5 per cent CO_2 + 95 per cent O_2 × 5 (*By courtesy of Biochemical Journal*)

FIG 99 —Perforations in a frog gastric mucosa after 5 hours stimulation with histamine in phosphate saline gassed with 100 per cent O_2 × 25 (*By courtesy of Biochemical Journal*)

FIG 100 —Living isolated tubules from polecat gastric mucosa secreting neutral red The canaliculi of the oxyntic cells contained neutral red in the acid form Slight alterations of the focus showed the basketwork of canaliculi connected together in the cells × 330 (*By courtesy of Biochemical Journal*)

FIG 101 —Development of ulceration in frog gastric mucosa after 4 hours stimulation with histamine in phosphate saline gassed with 100 per cent O_2 5μ section in formol zenker stained with haematoxylin and eosin × 55

respiration of the pyloric antrum is not increased by histamine and it seems probable that the increased rate of respiration of gastric mucosa following stimulation by histamine is related solely to the process of acid secretion

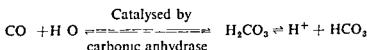
A comparison was made of the simultaneous rates of acid secretion and of the increased respiration in a series of 34 isolated frog gastric mucosae (Crane and Davies 1951) In all cases the ratio of molecules of acid produced to molecules of oxygen utilized was less than 13 One third had ratios not significantly different from 13 two thirds had ratios between 6 and 13 and only 1/[illegible] had ratios significantly less than 4

Even if the whole of the respiration of the mucosa and not just the increment on acid secretion is compared with the acid secretion during the same period then the acid is still formed at a much greater rate than the oxygen utilized (Davies 1948 Teorell 1949 Crane and Davies 1951)

Oxyntic cells require much more carbon dioxide than can be supplied from the normal metabolic output of the whole of the stomach This is of interest because it means that the actively acid secreting stomach requires not only external supplies of oxygen but even greater external supplies of carbon dioxide Therefore during high rates of acid secretion the stomach is removing both oxygen and carbon dioxide from the arterial blood and has a negative respiratory quotient (Davies 1948 Teorell 1933 Kurtz and Clark 1947 Furst Langfeldt and Morstad 1950) The problem of this carbon dioxide uptake has attracted much attention

THE ROLE OF CARBONIC ANHYDRASE IN ACID SECRETION

Carbonic anhydrase is a zinc containing enzyme which catalyses the first part of the following reaction which is normally relatively slow



$$CO_2 + H_2O \xrightleftharpoons[\text{carbonic anhydrase}]{\text{Catalysed by}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

This enzyme occurs in many parts of the body and is found in high concentrations in erythrocytes where as Roughton (1943) has shown it plays an essential role in carbon dioxide transport in the blood

Davenport and Fisher (1938) found this enzyme in the stomach and Davenport (1939) showed that there are large amounts of this enzyme in the oxyntic cells This led to the suggestion that carbon dioxide arising in the cells from the combustion of a metabolite is hydrated to carbonic acid under the influence of carbonic anhydrase and that the ionization of this acid was the source of the hydrogen ions This suggestion was valuable because it stimulated much work which showed that although the carbonic anhydrase theory of acid secretion was incorrect as originally stated the enzyme carbonic anhydrase plays a role in the overall processes of acid secretion

An important part of the carbonic anhydrase theory was that this enzyme was needed to facilitate the formation of the hydrogen ions and therefore that inhibition of the enzyme should lead to inhibition of gastric secretion The experimental situation has been very confused in the last 10 years Davenport (1940) soon found that thiocyanate could inhibit both acid secretion and carbonic

anhydrase and this seems strong support for the theory However it was shown by Feldberg, Keilin and Mann (1940) that the much more powerful inhibitor of carbonic anhydrase sulphanilamide failed to inhibit acid secretion although it certainly inhibited the enzyme much more than did the thiocyanate Davenport (1946) later obtained similar results with even more powerful inhibitors and withdrew the theory

At this stage Davies and Roughton (1948) calculated from the known rates of acid secretion and Davenport s figures for the carbonic anhydrase content of oxyntic cells that (1) the rate of acid secretion and hence of carbon dioxide uptake in both isolated frog gastric mucosa and in the intact mammalian stomach was so great that carbonic anhydrase activity was required to catalyse the hydration of the carbon dioxide and (2) the amount of carbonic anhydrase activity present in oxyntic cells is apparently in large excess of that required to perform the necessary magnification of the uncatalysed carbon dioxide uptake Thus complete inhibition of the carbonic anhydrase should lead to the accumulation of un neutralized alkali and therefore damage the cells and stop acid secretion However all these attempts to inhibit acid secretion by inhibiting carbonic anhydrase *in vivo* have failed These experiments were done on cats dogs and turtles and although most of the carbonic anhydrase was found to be inhibited at the end of the experiment when extracts were made of the ground up stomachs there is good reason to believe that the enzyme was not completely inhibited in the functioning oxyntic cells Red blood cells contain only about ½ as much carbonic anhydrase as oxyntic cells and if the enzyme had been inhibited by more than the 99 7 per cent required to inhibit acid secretion carbon dioxide transport by the blood would have been so seriously interfered with that the animals would have died All the animals were in fact alive which is good evidence that the enzyme was not completely inhibited *in vivo*

Although only about 0 3 per cent of the enzyme activity is required experiments with mucosa *in vitro* have shown that complete inhibition of the carbonic anhydrase can lead to inhibition of acid secretion and to cell damage In isolated tissues blood is not required to take part in oxygen and carbon dioxide transport and so direct effects of the inhibitors on the processes of acid secretion can be studied A significant depression of gastric acid secretion in the presence of the rather toxic thiophene 2 sulphonamide was obtained by Davenport and Jensen (1948) who used isolated mouse stomach and complete inhibition was obtained by Davies and Edelman (1948) who used some highly effective reversible carbonic anhydrase inhibitors such as *p* toluenesulphonamide and Prontosil soluble on isolated frog gastric mucosa These inhibitors have no effect on the non secreting mucosa nor on a variety of other tissues but inhibited acid secretion and respiration after a lag period This is to be expected if the function of carbonic anhydrase is to prevent an accumulation of un neutralized alkali within the oxyntic cells There was only a slight inhibition of acid secretion during the first half hour after the addition of the inhibitors but complete inhibition during the next half hour and subsequently This time would be needed for a damaging amount of alkali to accumulate Estimations of the carbonic anhydrase activity of these mucosae made at the end of the experiment showed that it was then completely inhibited It is interesting that in these experiments where the uptake

of carbon dioxide had been prevented by *interfering with the enzymic processes* ulcerations and perforations of the mucosa were observed Such ulcerations and perforations also occurred when the isolated mucosa was stimulated to secrete acid in the absence of external supplies of carbon dioxide (*see* Figs 99 and 101 (page 274) The *alkali* accumulating in the oxyntic cells under such conditions is believed to be the cause of the tissue damage (Davies and Longmuir 1948)

Carbonic anhydrase activity is present in oxyntic cells in what seems to be an enormous excess as less than 1 per cent of it is required by the cells The maximum rate of acid secretion by mammalian oxyntic cells can be compared with the turnover number of the sort of enzymes believed to take part in the mechanism of secretion This gives a value for the number of secretory units in each oxyntic cell This figure of about 10^7 is virtually the same as the number of carbonic anhydrase molecules present in each oxyntic cell It seems very reasonable that there is one or only a very few molecules of carbonic anhydrase associated with each of the enzyme arrays which constitute the secretory unit However carbonic anhydrase has a *very high turnover number relative to the hydrogen transporting* enzymes and this may well account for the apparent excess of activity If there is only one molecule of carbonic anhydrase for each secretory unit then a 99 per cent inhibition of the enzyme might be expected to produce a 99 per cent inhibition of *acid secretion However this does not follow because in a reversible system* 99 per cent inhibition does not mean that only 1 in a 100 of the molecules is active and the rest are inactive but that all the enzyme molecules are inactive for 99 per cent of the time Thus during the 1 per cent of the time the molecule is active in these circumstances it can catch up its arrears and maintain the *local* acid base balance The apparent excess is therefore only of carbonic anhydrase activity and not of carbonic anhydrase molecules

THE SOURCE OF THE HYDROGEN AND *CHLORIDE IONS*

During the past few years there has been a revival of the old idea of Maly (1874) that the hydrogen ions might come from the ionization of an organic acid This view has been put forward by Bull and Gray (1945) and Conway FitzGerald and Walls (1945) In the original form of the theory it was believed that the acid was lactic pyruvic or phosphopyruvic formed during the oxidation of glucose within the oxyntic cells This is impossible because of the observed rates of acid secretion relative to the rate of oxygen uptake (Davies 1948 Crane and

TABLE II

THE NUMBER OF HYDROGEN IONS FROM THE IONIZATION OF CARBONIC OR PYRUVIC ACIDS FORMED DURING GLUCOSE OXIDATION

O_2		C H O glucose	$6O_2$	
↓ $2CH_3$ CO COOH pyruvic acid			↓ 6H CO carbonic acid	
$2CH_3$ CO COO^-	→	+2H		
$5O_2$				
6HCO	→	+4H	6HCO	6H

Davis 1951) *One molecule of glucose can form only two molecules of pyruvic acid and six molecules of oxygen are required to complete the oxidation to carbon* dioxide and water This means that if the hydrogen ions arise from the organic acids during the normal processes of aerobic oxidation the rate of acid secretion could never be more than ⅓ the rate of oxygen uptake The carbonic anhydrase theory required that the hydrogen ions came from the hydration of the carbon dioxide followed by subsequent ionization In this case the rate of acid secretion could never be greater than the rate of oxygen uptake (*see* Table II) The observation that the rate of acid secretion could be many times greater than the rate of oxygen uptake thus rules out both theories

In late modifications of the organic acid theory by Conway the acid acts as a carrier so that most and perhaps all the hydrogen ions of the hydrochloric acid then come initially from the hydrogen atoms present in water This conclusion is required by the experimental results Although some of the hydrogen ions could come from glucose water is the only material which can supply sufficient and equivalent amounts of acid and alkali to account for the rate at which hydrochloric acid can be secreted by the stomach

When blood passes through an actively acid secreting stomach there is a quantitative exchange of bicarbonate and chloride ions and this leads to a reversed chloride shift (Gray 1942) This means that the chloride ions of the hydrochloric acid come from the chloride ions within the red blood cells which are released in exchange for bicarbonate ions a process which also requires carbonic anhydrase activity

Oxygen is essential for the processes of acid secretion since in its absence no hydrochloric acid is formed Normally the cells oxidize glucose but several of the compounds formed during the breakdown of glucose will also support acid *secretion These include pyruvate* lactate *and acetoacetate* (Davenport and Chavre 1950) *It seems likely that the energy from the oxidation of* these compounds is utilized for the production of high energy phosphate bonds and that the energy from these bonds is directly used to form hydrochloric acid Further discussion of this point will be postponed until consideration is given to another line of investigation of the problem

THE ELECTRICAL ACTIVITY OF GASTRIC MUCOSA

Many organs of the body have the power to produce electric currents Donné (1834) first found that there was a potential difference across the wall of the stomach since when there has been a large amount of work on the possible relations between the functional activity and electrical phenomena in the stomach Much of the early work was primitive and uncontrolled and along with animal *magnetism* the whole topic fell into disrepute and has only been revived in the last 10 years (*see* reviews by Crane 1950 and Rehm 1950) Most of this work has come from Rehm and his colleagues in Louisville and from the Sheffield laboratories Rehm used flaps of the wall of a dog s stomach whilst work from the Sheffield laboratories has centred on the use of isolated sheets of frog and toad gastric mucosa The fundamental similarity of major biochemical processes is demonstrated by the fact that despite the great differences in biological material the two groups of workers have obtained similar results on all major points

The resting mucosa maintains a potential difference between identical electrodes in identical solutions on the two sides of the mucosa with the secretory side negative to the nutrient side in an external circuit This potential difference is about −70 millivolts across the dog s stomach and about −30 *millivolts across the* isolated frog gastric mucosa In isolated frog gastric mucosa the potential difference measured between two glass or silver-silver chloride electrodes was found to vary systematically with the concentration of hydrogen and chloride ions respectively *in the secretory solution In both cases there was included* an asymmetry potential of the same sign and magnitude as was observed when calomel electrodes were connected to the two solutions by salt bridges of saturated potassium chloride solution This asymmetry potential varies in magnitude with the concentration of alkali-metal cation on the secretory side This can be interpreted as showing that the resting stomach is largely impermeable to hydrogen and chloride ions and is behaving in a similar way to a sodium electrode

The potential difference across the stomach is not a static phenomenon like an electric double layer because it can do work and its maintenance depends on aerobic metabolism It is abolished in the absence of oxygen or in the presence of inhibitors of respiration or phosphorylation When the two sides of gastric mucosa are connected electrically a current can be maintained for hours This requires the continuous performance of electrical work and under some conditions this current may consist entirely of the movement of sodium ions When secretion commences following the addition of histamine there is a fall in the potential *difference across the mucosa However when secretion is well established large* increases in the rate of secretion are associated with only small changes in the potential difference These changes are reversed when secretion stops

An important observation is that the rate of acid secretion can be altered in a polar manner by *the passage of electric current through the mucosa Currents* (*c* 1 milliampere per square centimetre) passed through the mucosa from an external battery in such a direction as to increase the natural potential difference across the stomach increased and even doubled the rate of acid secretions Currents in the opposite direction decreased and could completely abolish the rate of secretion Passage of current does not initiate secretion in the dog but may do so in the frog Such currents formed no acid when passed through a large variety of natural and artificial secretory or non secretory live or dead biological membranes

It is unfortunate that oxyntic cells are very inaccessible and are embedded in a much greater volume of non secretory tissue The interpretation of changes in electrical parameters is thus made difficult This is especially so when attempts are made to draw quantitative conclusions from the experimental results However the electrical behaviour of gastric mucosa is consonant with the mechanism of acid secretion which has recently been put forward (Davies and Ogston 1950 and Rehm 1950) It seems probable that acid secretion and the production of electric current are linked properties of oxyntic cells and the enzyme systems responsible for one also lead to the production of the other

When an electric current is forced through two hydrogen electrodes in a salt solution electrical energy is used At one electrode electrons are removed from the hydrogen atoms in the hydrogen gas so that hydrogen ions are formed At the

other electrode hydroxyl ions are formed It is believed that a closely similar process occurs in oxyntic cells Biochemical energy is used so that near the canalicular wall electrons are removed from the hydrog n atoms in a reduced carrier to form hydrogen ions together with the oxidized carrier When the carrier is reduced again hydroxyl ions are formed by a removal of hydrogen ions from water

ENERGY RELATIONS IN GASTRIC MUCOSA

Thermodynamics can sometimes be used to throw light on the mechanism of biological processes In the case of hydrocnloric acid production by the stomach it is possible to calculate the minimum free energy required to raise the chemical potential of hydrogen ions in equilibrium with blood to the chemical potential of hydrogen ions in equilibrium with gastric juice This works out at about 9 500 calories per gram molecule of hydrochloric acid and this figure is quite independent of the actual mechanism by which the acid is produced If the actual process is inefficient then more than 10 000 calories would be required It is also possible to calculate the maximum free energy that could be available from the oxidation of glucose under physiological conditions This amount of energy will only be available if the processes of utilization are 100 per cent efficient and works out about 116 000 calories per gram molecule of oxygen

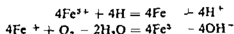
If both the utilization of the energy from oxidation as well as the processes involved in the formation of the hydrochloric acid are 100 per c nt efficient then the maximum possible ratio of molecules of acid formed per molecule of oxygen will be about 12 in mammals and 13 in amphibia It is remarkable that this figure is actually reach d when the amount of acid secreted by isolated frog gastric mucosa is compared with the extra oxygen uptake of the tissues which occurs during the secretion

If the mechanism in man is completely efficient then the secretion of 1 litre of pure gastric juice containing 0 16 molar hydrochloric acid requires a free energy expenditure of 1 500 calories (1 5 Calories) and to do this 300 millilitres of oxygen and 3 600 millilitres of carbon dioxide are used by the oxyntic cells which weigh only about 6 grams in an average man

However the energy relations alone are not a sufficient basis on which to put forward a mechanism for hydrochloric acid secretion It is necessary to consider the actual chemical processes which could be involved

THEORY OF HYDROCHLORIC ACID FORMATION

The electrical phenomena show that the stomach is an organized arrangement of polar units Since the oxynetic cells secrete hydrochloric acid in one direction only the enzyme arrays of the secretory units in the pericanalicular zone of these c lls must therefore be orientated in space Respiration generally involves the participation of a catalyst or several catalysts in which ferric and ferrous ions are periodically interconverted This means that respiring cells possess a mechanism whereby hydrogen and hydroxyl ions are continuously formed as shown below



$$4Fe^{3+} + 4H = 4Fe \quad + 4H^{+}$$
$$4Fe^{\ +} + O_2 - 2H_2O = 4Fe^{3} \quad - 4OH^{-}$$

where H represents a hydrogen atom of the substrate molecule or of water and O_2 molecular oxygen This means that the overall reaction for glucose oxidation may be formulated as follows



$$C_6H_1\ O_6 + 18H\ O + 6O \longrightarrow 6CO\ + 24H^+ + 24OH^-$$

Since a series of iron compounds known as the cytochromes–cytochrome oxidase system takes part in respiration it may be expected that the formation of hydrogen and hydroxyl ions would not occur at the same iron atom but at some distance from each other In most cells the valency changes of the ferrous–ferric system are probably balanced by movement of the hydroxyl ions along this array of cytochromes so that they react with the hydrogen ions to form water However if these sites are separated by an impermeable structure in oxyntic cells then hydrogen ions would be available for secretion as hydrochloric acid and the valency changes satisfied by movement of chloride ions By this mechanism alone only four hydrogen ions can be secreted for every oxygen molecule used during respiration It seems most unlikely that this is the case If the extra oxygen uptake following the addition of histamine to an isolated gastric mucosa is compared with the acid produced in the same period it is found that up to about 12 hydrogen ions are formed for each oxygen molecule utilized Another objection discussed earlier is that the rate of acid secretion of the intact mammalian stomach can be so enormous that incredibly high values of the oxygen uptake would be needed if the hydrogen ions were formed by this mechanism alone The free energy changes in the final stages are sufficient to form hydrochloric acid at the observed concentration but the processes are probably more complex and involve intermediate phosphorylations (Davies and Ogston 1950)

Recent developments in biochemistry have shown that in many cases the best explanation for the experimental observations is that energy is used by cells not in a large number of forms but probably in one form only The energy needed to carry out a large variety of chemical mechanical and osmotic processes all seems to come from special types of chemical compounds containing what are known as high energy phosphate bonds Since oxyntic cells are only about ⅓ of the dry weight of gastric mucosa it is difficult to distinguish the metabolism of these cells from the rest of the tissue However the use of specific inhibitors in particular 2 4 dinitrophenol on the isolated gastric mucosa has given some information This compound has the power of uncoupling the oxidative processes which normally lead to the production of high energy phosphate bonds and it has been found that it completely inhibits gastric acid secretion and abolishes the electric potential although the respiration rate is unaffected or actually increased This suggests that the hydrogen ions produced directly during respiration are only secreted after further processes involving phosphorylation (Davies and Ogston 1950) It is of interest that these high energy phosphate bonds contain enough energy to account for the formation of the hydrochloric acid and in the case of creatine phosphate the energy released by splitting this bond could result in the formation of two molecules of hydrochloric acid

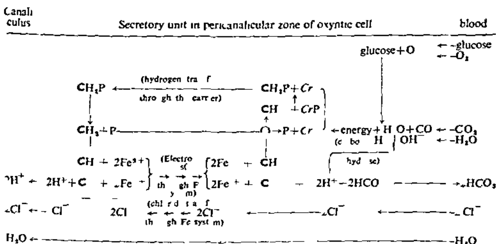
The problem of the source of the hydrogen ions of the gastric secretion has been discussed earlier The hydrogen atoms transferred by the respiratory catalysts

during the normal course of oxidation of glucose are not sufficient The only other course is water and this compound can form sufficient amounts of acid and alkali to account for acid secretion by the stomach provided enough energy is made available

The formation of hydrogen and hydroxyl ions from water requires the separation of charges so electrical work must be done and this formation of ions whether by electrolysis or otherwise is equivalent to an oxido reduction as electrons are removed from one part of the water molecule and transferred to the other

Some of the details of any theory of hydrochloric acid secretion must of necessity be somewhat speculative at the present state of our knowledge but it is possible to present a mechanism which accounts for the known observations and can be used as a guide for further experimental work The basis of such a process has been given in the electron-cycle mechanism of gastric secretion (Crane Davies and Longmuir 1948) This process requires (1) a means of transporting hydrogen atoms (electrons + protons) across the pericanalicular zone of the oxyntic cells (2) a means of returning the electrons to the starting point near the cell wall and (3) a source of power sufficient to drive the processes for acid formation (Table III)

TABLE III



Scheme of the mechanism of hydrochloric acid secretion (The hydrogen ions are derived ultimately from water C and CrP represent creatine and creatine phosphate **C** and **CH** the hydrogen carrier and its reduction product These might be oxaloacetate and L malate)

All these are known to occur in living cells The extra requirement for this theory is that all the systems are suitably arrayed in space A series of enzymes and their substrates involved in dehydrogenation could account for (1) in

particular the enzyme substrate responsible for hydrogen transport could be the system oxaloacetate $\underset{-2H}{\overset{+2H}{\rightleftharpoons}}$ L malate A coupled cytochrome or cytochrome like system could be (2) and (3) could be the energy from high energy phosphate bonds

A unit cycle can now be described Two hydrogen ions formed from two water molecules near the cell wall oxidize ferrous to ferric ions in the cytochrome system and by accepting the electrons are reduced to hydrogen atoms These hydrogen atoms react with oxaloacetate to form L malate which further reacts with a high energy phosphate bond There is in fact evidence that this reaction normally involves a phosphorylating mechanism (Ruffo and Cennamo 1946) The concentration of this complex now builds up and it diffuses to the region near the canalicular wall where two hydrogen ions are liberated by the reconversion of L malate to oxaloacetate with the reduction of ferric to ferrous ions by the electrons and the liberation of inorganic phosphate The resultant hydrogen ions pass into the canaliculus together with the chloride ions released by reduction of the ferric ions from the trivalent to the divalent state The electrons from the hydrogen atoms are returned by the ferrous–ferric system to the other end of the secretory unit and pass round the cycle again Valency requirements are satisfied by the movement of a chloride ion in the opposite direction to the electron

The net effects of the process are the hydrolysis of high energy phosphate bonds the transport and secretion of hydrochloric acid and the formation of hydroxyl ions which following the uptake of carbon dioxide react to form bicarbonate ions as discussed previously Kinetic and thermodynamic considerations show that creatine phosphate could act as the source of energy and that the hydrogen and electron transfer systems could be oxaloacetate—L malate and cytochrome B or perhaps fumarate succinate and cytochrome C Histamine has the kind of chemical structure that could act by changing permeability barriers and thus initiate secretion by allowing the hydrogen ions to leave the cell (Crane Davies and Longmuir 1948 Davies and Ogston 1950) A more detailed investigation of the mechanism shows that the electrical potential differences observed across the mucosa and the effect of passing current through the mucosa could be accounted for by this theory It should be pointed out that although this theory can explain the known observations it may need modification in the light of further researches

The problem of the water of the gastric juice has received relatively little attention It has been thought that blood pressure was required to move the water from the blood to the stomach but this is certainly untrue because isolated gastric mucosa can secrete against a net pressure The secretion of water must be linked in some way with acid secretion by the stomach It is of interest that 350 molecules of water are secreted with each molecule of hydrochloric acid This has an important bearing on the processes involved The rate of formation of hydro chloric acid can be enormously fast compared with the rates of other metabolic processes in mammalian cells and as the rate of transport of water must be 350 times faster still this rules out the possibility that water molecules are handled one by one by enzyme systems in the cells they must be transferred in bulk (For further discussion *see* Davies 1951) The rate of exchange of water across

the stomach is very rapid compared with the rate of secretion as has been shown in experiments with heavy water and as oxyntic cell secretion is normally about isotonic with the blood it seems most likely that the transfer of water follows osmotically as a result of the active secretion of hydrochloric acid and is not a separate process

SUMMARY

Hydrochloric acid is formed as such by oxyntic cells and is secreted without precursor in the intracellular canaliculi Gastric juice as found in the stomach is however a complex mixture Recent developments have depended largely on the application of biochemical techniques in particular those used for the study of isolated tissue Acid secretion cannot be observed when sheets of gastric mucosa are incubated in a saline solution but can be studied when the tissue is incubated in the form of tied tubes For every molecule of hydrochloric acid secreted there is an uptake of one molecule of carbon dioxide and a bicarbonate ion is liberated into the nutrient medium in exchange for a chloride ion When acid secretion commences there is an increase in the rate of respiration and up to about 12 hydrogen ions are secreted for each extra oxygen molecule used The uptake of carbon dioxide by secreting oxyntic cells is greater than the carbon dioxide output of even the whole stomach and supplies of this gas must be provided by the arterial blood during high rates of acid secretion This uptake of carbon dioxide is so rapid that the process must be catalysed by the enzyme carbonic anhydrase There is sufficient of this enzyme present in the oxyntic cells to account for the rate of carbon dioxide uptake and when the enzyme is completely inhibited or when carbon dioxide is removed from the apparatus cell damage occurs and acid secretion is inhibited following the accumulation of un neutralized alkali within the oxyntic cells The rate of acid secretion is so great relative to the rate of respiration that many of the theories of acid secretion which have been proposed are at once ruled out Although part of the hydrogen ions could come from glucose and the water incorporated in it during its oxidation water is the only source which can account for the number of hydrogen ions secreted and the simultaneous production of hydroxyl ions The stomach can act as an electric battery and even *in vitro* can maintain a continuous electric current for hours Changing the potential across an acid secreting stomach can increase or decrease the rate of acid secretion and changes in the electrical parameters of the stomach closely follow changes in the secretory activity It is remarkable that the stomach has a very high efficiency in transferring energy from the processes of oxidation to those required for the production of acid This efficiency may even approach 100 per cent On the basis of the present knowledge of the metabolism of gastric mucosa a theory of acid secretion is presented in which the energy from high energy phosphate bonds is utilized to form hydrogen ions and hydroxyl ions from water The enzyme system is believed to be so oriented in space that the hydrogen ions formed are secreted as hydrochloric acid and the hydroxyl ions neutralized to form bicarbonate ions and exchanged across the cells wall for chloride ions from the blood It seems probable that the secretion of water by the oxyntic cells follows the secretion of hydrochloric acid by a straightforward osmotic process

I wish to thank Professor H A Krebs and Mr H L Kornberg for many helpful suggestions made during the preparation of this section

REFERENCES

Babkin B P (1950) *Secretory mechanism of the digestive glands* 2nd ed New York Hoeber
Bence Jones H (1845) *Philos Trans* **135** 335
Bernard C (1858) *Propriétés physiologiques des liquides de l organisme* Paris Baillière
Bradford N M and Davies R E (1950) *Biochem J* **46** 414
Bull H B and Gray J S (1945) *Gastroenterology* **4** 175
Conway E J FitzGerald O and Walsh D (1945) *Nature Lond* **156** 477
Crane E E (1950) Bioelectric potentials their maintenance and function In *Progress in Biophysics* London Butterworth Springer
— and Davies R E (1951) *Biochem J* **49** 169
— — and Longmuir N M (1948) *Ibid* **43** 321
Davenport H W (1939) *J Physiol* **97** 32
— (1940) *Amer J Physiol* **129** 505
— (1946) *Physiol Rev* **26** 560
— and Chavré V J (1950) *Gastroenterology* **15** 467
— and Fisher R B (1938) *J Physiol* **94** 16P
— and Jensen V (1948) *Gastroenterology* **11** 227
Davies R E (1948) *Biochem J* **42** 609
— (1951) *Biol Rev* **26** 87
— and Edelman J (1948) *Biochem J* **43** 57
— and Longmuir N M (1948) *Ibid* **42** 621
— and Ogston A G (1950) *Ibid* **46** 324
— and Roughton F J W (1948) *Ibid* **42** 618
Delrue G (1930) *Arch int Physiol* **33** 196
Donne A (1834) *Ann chim (Phys)* **57** 398
Engstrom A and Glick D (1950) *Science* **111** 379
Feldberg W Keilin D and Mann T (1940) *Nature Lond* **146** 651
Fisher R B and Hunt J N (1950) *J Physiol* **111** 138
Furst V jun Langfeldt E and Morstad O (1950) *Acta physiol scand* **21** 278
Gray J S (1942) *Fed Proc* **1** 255
Hollander F (1943) *Gastroenterology* **1** 401
Kurtz, L D and Clark B B (1947) *Ibid* **9** 594
Maly R (1874) *Liebigs Ann* **173** 227
Prout W (1824) *Philos Trans* **144** 45
Rehm W S (1950) *Gastroenterology* **14** 401
Roughton F J W (1943) *Harvey Lect* **39** 96
Ruffo A and Cennamo C (1946) *Arch Sci biol Napoli* **31** 127
Teorell T (1933) *Skand Arch Physiol* **66** 225
— (1949) *Experientia* **5** 409

SECTION II

HORMONAL CONTROL

R A GREGORY

IN ANY discussion of the role of hormones in the control of gastric secretion it is essential first to define clearly certain terms in current usage in this field for a good deal of confusion is evident in the literature in regard to the precise significance of these terms and therefore their proper usage These are (1) hormone (2) humoral agent and (3) secretagogue The word hormone will be used in this review in its usual sense of a specific substance elaborated by certain cells in the body and carried by the blood to other cells the activity of which it either stimulates or restrains It is often uncertain whether or not a hormone thus defined is responsible for the influence which one region of the alimentary canal can be shown to exert upon another by way of the blood stream and in such cases the non specific designation humoral agent should be used until the nature of the agency responsible can be defined The use of this term is now largely confined in the field of endocrinology to the gastro intestinal tract and is necessitated there because of the fact that among the chemical stimuli normally concerned in the activation of the hormonal mechanisms which have been demonstrated to exist are substances derived from digestion of the food and it has been shown that such digestion products may themselves influence gastric secretion when slowly administered intravenously After absorption in the portal circulation during digestion they may therefore by their presence in the systemic blood act as humoral agents stimulating gastric secretion Such substances are conveniently termed secretagogues A humoral agent may thus turn out to be either a hormone or a secretagogue on further examination

The substances which will be considered here are (1) *gastrin* the hormone of gastric origin which excites gastric secretion (2) *enterogastrone* the hormone of upper intestinal origin which depresses both gastric secretion and motility and (3) certain other substances which are not as yet precisely defined in status but which are included because of their possible relationship to gastrin and enterogastrone These are (1) The intestinal humoral agent which excites gastric secretion (2) urogastrone a substance present in urine which inhibits gastric secretion may be of small intestinal origin and is possibly a derivative of entero gastrone and (3) anthelone a substance present in urine which is apparently without effect upon gastric secretion but which protects the upper intestinal mucosa in the dog from experimental peptic ulceration The chemical nature of all these substances is ill defined although the available evidence suggests that they are proteins

Physiological studies indicate that the gastric hormone is certainly present in the pyloric region and probably also in the rest of the stomach Similar evidence

indicates that enterogastrone is present in decreasing amount from the pyloric sphincter downwards and that the lower two thirds of the small intestine contains relatively small amounts of the hormone However the cells in these regions which produce gastrin and enterogastrone have not yet been defined

Extracts of the mucosa of the appropriate portion of the alimentary tract have been prepared which produce effects on injection similar to—though not always identical with—those of the hormone which physiological evidence indicates is located there thus extracts from the pyloric region of the stomach and from the upper part of the small intestine can be shown to contain a stimulant of secretion which may be identical with or derived from the gastric hormone and the intestinal humoral agent Similarly extracts from the small intestinal mucosa contain an inhibitor of secretion and motility which may represent the hormone enterogastrone The active material is largely confined to the upper third of the small intestine so that it is not generally profitable to include the lower portion of the gut beyond this point in extraction procedures

Methods

In the case of endocrine organs outside of the alimentary tract the location of which is well defined the classical approach to the study of their functions is to remove them and observe the effects which result from their absence This is not possible in the alimentary tract because the ensuing functional disturbances obscure the effects of removing the site of origin of the hormone For instance removal of the pyloric region as the chief source of the gastric hormone leads to changes in the secretory response of the stomach to a meal which are referable not merely to the supposed loss of the hormone but also to changes in gastric emptying time and therefore alteration in the conditions of intestinal digestion with consequent alteration in the extent of the humoral and nervous influences exerted from the intestine on gastric secretion and motility This difficulty in the way of demonstrating the effects and indeed the very existence of certain of the alimentary tract hormones has led to the development of surgical techniques (Markowitz 1949) whereby some portion of the stomach or small intestine may be segregated in the form of a pouch or isolated loop so that a possible endocrine mechanism involving that region may be studied without major interference with the functions of the remainder of the alimentary tract The most valuable of such preparations is the transplanted pouch or intestinal loop which is devoid of its original nervous connections and can therefore influence or be influenced by the rest of the alimentary tract only *via* the blood stream that is by humoral mechanisms

THE GASTRIC HORMONE (GASTRIN)

The work of Pavlov (1910) and his contemporaries established the fact that the secretory response of the stomach to a meal involves three phases of stimulation (1) the initial or cephalic phase having the vagi as the efferent pathway for a reflex of conditional or unconditional nature (2) the gastric phase caused by the action upon some part of the gastric mucosa of the products of protein digestion formed from the food by the cephalic secretion and (3) an intestinal

phase caused by the presence in the small intestine of the gastric chyme It has also been recognized since that time that fat inhibits all three phases of stimulation by its presence in the upper part of the small intestine in the gastric chyme (Ivy and Gray 1937) The final secretory response of the stomach to a meal results therefore from the successive and to some extent superimposed effects of these three phases depressed in proportion as the meal contains fat and this enters the small intestine

Bayliss and Starling (1902) proved the existence of secretin by a series of experiments and inferences from them which have since become classical This work may have led Edkins (1906) to enunciate the gastrin theory to account for the second or gastric phase of the secretory response of the stomach to a meal Edkins prepared crude extracts from various regions of the gastric and small intestine mucosa which were injected into anaesthetized cats It was claimed that only pyloric mucosal extracts stimulated gastric secretion and it was suggested that this effect was due to the presence of a hormone which was normally liberated during gastric digestion by the action on the pyloric mucosa of protein digestion products Edkins experiments were open to grave objections on technical grounds and it was soon shown (Popielski 1909 1913 Rogers and others 1916 1919) that extracts from almost any tissue in the body contained a stimulant of gastric secretion This ubiquitous substance eventually turned out to be histamine (Popielski 1920) and the demonstration that all regions of the gastric mucosa contained large amounts of histamine (Gavin McHenry and Wilson 1933) led to the widely held view that if a gastric hormone existed it was most likely to be histamine

The many investigators who subsequently studied the secretory effects of extracts from the stomach and small intestine apparently in search of the gastric hormone do not appear to have been deterred by the paucity at that time of reliable physiological evidence as to its existence Certain experiments performed by Pavlov s pupils (Babkin 1928) were generally accepted as indicating that the pyloric region was the origin of the stimulation of secretion during digestion of food in the stomach (the gastric phase) but they did not in fact even indicate whether the mechanism was nervous or humoral much less prove that it was hormonal

Savitsch and Zeliony (1911 1913) showed that chemical or mechanical stimulation of the main stomach or the pyloric region caused a Heidenhain fundic pouch (vagally denervated) to secrete and that anaesthetization of the main stomach or pyloric region by the local application of cocaine prevented the response as also did the administration of atropine Their results again did not prove the existence of a gastric hormone but in fact appeared to show that the response was due to a nervous mechanism the probable explanation of the findings has been revealed by later work (Gregory and Ivy 1941 Robertson and others 1950)

Ivy and Whitlow (1922) tested the gastrin theory by preparing pouches of the fundic and pyloric regions in dogs and infusing into the pyloric pouch a variety of solutions which might be expected to liberate the hormone if one existed Their results were completely negative the fundic pouch did not respond The effect of this severe blow to the gastrin theory persisted for some years and the results are difficult to explain now that the existence of the hormone seems well established

but it may be noted that one stimulus in the pyloric region not employed was a mixture of food and gastric juice that is the presumably normal stimulus for liberation of the hormone Such an experiment has apparently never been performed

During the succeeding years a variety of evidence of a slender and often conflicting nature accumulated indicating that (1) the pyloric region was in some way concerned in the stimulation of secretion during the gastric phase of digestion and (2) that the mechanism involved was humoral For instance it was claimed by some (London 1913 1925 Smidt 1923 Portis and Portis 1926 Wilhelmj O Brien and Hill 1936) but denied by others (Shapiro and Berg 1934 Grindlay 1941) that removal of the pyloric antrum resulted in a considerable and persistent depression of the response of the stomach to a meal although the effects of antrectomy on the rate of gastric emptying and therefore upon the remaining mechanisms concerned in the response of the stomach to the meal made it difficult to draw any precise conclusions as to the cause Secondly stimulation of the pyloric region or main stomach by chemical agents or distension where the responding fundic pouch was probably denervated (Lim Ivy and McCarthy 1925) was sometimes shown to give a positive though slight reponse from the latter

The position in 1925 was that no generally acceptable physiological evidence existed for the presence of a gastric hormone in the pyloric or any other part of the stomach Such active gastric mucosal extracts as had been obtained apparently owed their stimulant effects on gastric secretion to their content of histamine the wide distribution of which in the body appeared to deprive it of any qualification to be considered as a gastric hormone in the absence of positive proof of its liberation from the stomach during digestion

A great step forward was achieved in the same year when Ivy and Farrell (1925) successfully transplanted a gastric pouch into the mammary region of a dog Such a pouch eventually comes to receive a blood supply from the surrounding tissue and although its secretory behaviour will naturally be influenced by the conditions of circulation in the site of transplantation and therefore by reflex vascular changes in this region it may safely be considered to be completely deprived of its original nervous connections and to secrete only in response to humoral agents reaching it by way of the blood stream

Ivy and Farrell observed that a small but definite secretion of free acid occurred from transplanted pouches in dogs following a meal This proved conclusively for the first time that a humoral agent of some description was circulating in the blood after a meal It did not however throw any light on the nature of the agent (that is whether it was a hormone or absorbed secretagogues) or on its origin (whether from some part of the stomach or the small intestine or both)

The nature and origin of the humoral agent causing secretion from a transplanted pouch after a meal was determined by Gregory and Ivy (1941) Dogs were provided with a transplanted gastric pouch of the fundic region and the remainder of the stomach made into a second pouch with anastomosis of the duodenum to the oesophagus It was shown that the introduction of secretagogues into the main stomach caused secretion from the transplant proving the existence of a gastric humoral mechanism The response of the transplant was prevented by

anaesthetizing the mucosa of the main stomach pouch with procaine before the application of secretagogues The application of procaine was shown not to prevent the absorption of other substances from the main pouch nor did it influence the response of the transplant to other humoral stimuli Therefore it apparently abolished the transplant response to secretagogues in the main pouch by preventing the liberation of a hormone presumably by blocking mucosal chemoreceptors which were stimulated by the secretagogues present in the main pouch

There was implicit also in these findings the suggestion that the release of the gastric hormone might be controlled by the local intrinsic nervous structures—the plexuses of Auerbach and Meissner If so then distension of the main stomach which had been shown by Lim Ivy and McCarthy (1925) to stimulate gastric secretion by a mechanism which was blocked by anaesthetizing the mucosa might also involve an intrinsic nervous mechanism and lead to liberation of the hormone as shown by a response of the transplant in the absence of secretagogues —direct proof of the existence of the gastric hormone Attempts by Gregory and Ivy (1941) to stimulate the transplant by distension of the main stomach failed but Grossman Robertson and Ivy (1948) later repeated this experiment with a positive result probably due to the use of larger and more sensitive transplants thus proving conclusively the existence of a gastric hormone

The work of Gregory and Ivy (1941) was closely followed by the publication of that of Uvnas (1942) who showed in acute experiments on cats that the effect of vagal stimulation on gastric secretion was due at least in part to the liberation of gastrin from the pyloric mucosa One difficulty in accepting these findings is that in dogs provided with vagally denervated (Heidenhain) pouches strong vagal *stimulation produced by insulin or sham feeding does not cause a significant* secretory response from the pouch although the remainder of the stomach responds vigorously (Jemerin Hollander and Weinstein 1943) If Uvnäs s theory is true generally gastrin should be liberated in such circumstances causing a response from the Heidenhain pouch

Very recently a third striking indication that the liberation of the gastric hormone from the pyloric region may be under the control of the intrinsic nervous mechanisms has come from the demonstration by Robertson and others (1950) that the application of a strong (1 per cent) solution of acetylcholine to the pyloric mucosa in conscious dogs causes secretion from the remainder of the stomach in the absence of the vagi Similar amounts of acetylcholine were inactive when injected subcutaneously and atropine prevented the response of the fundic region This seems a clear demonstration of the liberation from the pyloric region of a hormone causing secretion

There is thus increasing evidence showing that a gastric hormone exists and suggesting that its liberation may be under the control of the intrinsic nervous mechanism through which may operate such stimuli as vagal excitation local application of acetylcholine or secretagogues derived from the food and distension

The nature of the gastric hormone

Interest in the actions of gastrin extracts on secretion was given a strong stimulus by the work of Komarov (1938) Previously in the absence of definite evidence

to the contrary it had been assumed that if a gastric hormone existed it probably was histamine since attempts to extract a secretory excitant of non histamine nature from the gastric mucosa had failed (Sacks and others 1932 Gavin McHenry and Wilson 1933) and histamine was known to be present there in large quantities However Komarov prepared from pyloric mucosa a substance of protein character which was free of histamine but on intravenous injection into animals caused secretion of a highly acid juice having a low content of pepsin *that is a juice of the same character as that evoked by histamine* Unfortunately Komarov s work has not been consistently repeated successfully by some investi gators but Uvnas (1945) obtained active extracts by Komarov s method and Harper (1946) has extracted a substance with similar properties from gastric mucosa by a different method

Furthermore it has been shown that the gastric hormone liberated by the application of secretagogues to the stomach excites the secretion by a transplant of a juice of high acid and low pepsin content (Grossman Woolley and Ivy 1944) that is similar to that evoked by histamine Thus histamine the gastric hormone *liberated by physiological* experiments and histamine free gastrin *extracts* prepared by two different methods (Komarov and Harper) all cause secretion of the same type of juice It is tempting to conclude that the gastric hormone is a protein having secretory effects similar to those of histamine and that gastrin *extracts such as those of* Komarov and Harper owe *their effects to its presence* On the other hand the gastric mucosa contains large amounts of histamine and very little histaminase (Best and McHenry 1930) and the work of Emmelin and Kahlson (1944) and others indicates that the gastric glands are sensitive to extremely minute concentrations of histamine in the circulating blood It remains a possibility therefore that the gastric hormone is in fact histamine and that gastrin extracts owe their activity to the presence of a protein which liberates histamine from the tissues The crucial point is obviously the nature of the active substance normally released from the gastric mucosa—is it histamine or not?

Unfortunately pharmacological methods for the assay of histamine in *plasma* are not yet sufficiently sensitive to enable an answer to be given to this question by comparison of the histamine activity of the plasma before and after meals (Gregory 1950) Histaminase preparations have been used to try to clarify the situation *thus Komarov s gastrin* was found by Bauer and Uvnas (1944) to be resistant to histaminase *in vitro* and on the other hand Grossman and Robertson (1948) showed that a potent histaminase preparation inhibited the response of dogs to a meal Unfortunately the significance of the results is doubtful because of uncertainty regarding the purity activity *in vivo* and specificity of histaminase preparations It is clear that whether the gastric hormone is *in fact histamine* or not must depend upon further work for example identification of the substance liberated into the circulation in physiological experiments

THE INTESTINAL HUMORAL AGENT

Pavlov (1910) claimed to have been the first to observe that gastric secretion could be excited by the presence of food in the small intestine but no details of his work are available Le Conte (1900) introduced various food substances into the duodenum of dogs provided with gastric and duodenal fistulae and obtained

a small secretion of gastric juice The scanty response and the apparent difficulty of eliciting it led Pavlov and his contemporaries to neglect this phase of the secretory response to a meal although Fremont in Pavlov s laboratory evolved an excellent preparation for the study of this phase namely the pouch of the entire stomach with anastomosis of the oesophagus to the small intestine Fremont s results with such dogs are not available but Lim Ivy and McCarthy (1925) were the first subsequently to prepare such pouches and to show that when a meal was fed a considerable secretion of juice occurred from the stomach The response began more promptly and was greater if the food had been pre digested indicating that stimulation was due to products of digestion Gregory and Ivy (1941) prepared dogs with transplanted fundic pouches and the remainder of the stomach made into a pouch with anastomosis of oesophagus to duodenum When the animals were fed *the transplant responded indicating the liberation of a humoral agent* for stimulation of gastric secretion from the intestine but its nature (whether absorbed secretagogues or a hormone) has not yet been further investigated although Harper (1946) has prepared histamine free extracts from the small intestinal mucosa which stimulate gastric secretion on injection

ENTEROGASTRONE

When a meal containing fat is fed to humans (Ewald and Boas 1886) or animals gastric secretion is depressed and emptying retarded These effects are mediated from the intestine and are not due to a local action of fat in the stomach (Sokolov 1904) The participation of a humoral mechanism is indicated by the observation that fat in the intestine inhibits motility (Farrell and Ivy 1926) and secretion (Feng Hou and Lim 1929) in a transplanted gastric pouch The fact that the intravenous injection of chyle (containing neutral fat and digestion products associated with it) does not inhibit either gastric secretion (Feng Hou and Lim 1929) or motility (Quigley Zettleman and Ivy 1934) proves that the humoral agent is a hormone named enterogastrone by Kosaka and Lim (1930)

Extracts prepared by various methods from the small intestinal mucosa (Kosaka and Lim 1930 Gray Bradley and Ivy 1937 Ivy Grossman and Bachrach 1950) inhibit gastric secretion and motility on injection and are presumed on this account to contain the hormone enterogastrone The grounds for this presumption are slender While the evidence from physiological experiments that a hormone (enterogastrone) exists is satisfactory there is no information whatever regarding the chemical nature of the substance liberated into the circulation and substances which inhibit gastric secretion and motility on injection are of wide occurrence for example pyrogens of bacterial origin (Necheles 1945) Furthermore certain anomalies exist in the actions of enterogastrone extracts compared with those of the hormone liberated in physiological preparations Fat in the small intestine inhibits secretion and motility in all types of gastric pouch including transplants Enterogastrone extracts however do not inhibit motility in vagally denervated pouches Finally Ivy Grossman and Bachrach (1950) report that their latest enterogastrone extract prepared for clinical trial has only a comparatively small effect on motility compared with earlier extracts It seems doubtful as yet whether the substance present in such extracts bears any relation to the actual hormone

UROGASTRONE AND ANTHELONE

These substances are conveniently discussed together because of their probable close relationship Neither has been isolated and the physiological status of each is uncertain Detailed reviews of the problem have been made by *Sandweiss (1945)* Grossman (1950) and Ivy Grossman and Bachrach (1950)

Both are extractable from male and female human urine pregnant or non *pregnant Neither is identical with the gonadotrophic hormone or prolactin*

Anthelone is characterized by the resistance to jejunal ulceration produced in Mann Williamson dogs after repeated injections at a dosage effective in this way gastric secretion is not depressed It is claimed that the anthelone activity of urine extracts from various sources is in the following order pregnant ♀ > non pregnant ♀ > normal males > ulcer patients It has been suggested that the protective effect of anthelone injections in Mann Williamson dogs is due to the stimulation of fibroblastic proliferation new formation of blood vessels and epithelization of the mucosa

Urogastrone is a depressant of gastric secretion and (to a much smaller extent) of gastric motility isolated from normal human male urine and canine *urine* by Gray and *others* (1942) *It has been differentiated from pyrogen certain* sex hormones posterior pituitary hormone and kallikrein The suggestion has been made that it may be an excretion product of enterogastrone but there is no *reliable evidence* for or against this view The origin of urogastrone in the body is however uncertain after enterectomy in dogs it does not entirely disappear from the urine and it has been claimed that removal of the pituitary is followed by greatly diminished excretion However it must be borne in mind that no evidence has yet been brought to show that any method so far used for the isolation of enterogastrone urogastrone or anthelone gives consistent and satisfactory recovery of the activity originally present in the urine or mucosa so that the changes in amounts of these substances described must be viewed with great reserve

This brief review of the history of anthelone enterogastrone and urogastrone shows the confused situation which at present exists due chiefly to the difficulties of assaying the activities of extracts and therefore of isolating and identifying the substances concerned The greatest single obstacle is perhaps the lack of a chemical test for any of these substances Enterogastrone and urogastrone have similar *effects on gastric secretion* and motility and the latter may be derived from or even identical with enterogastrone Extracts of both have anthelone activity so that Sandweiss principle may be related to either or a contaminant in each *case It seems to be* well established that Sandweiss anthelone extract does not exert its protective effects against experimental ulceration by depressing secretion or motility although it may possibly act by counteracting an abnormal stimulus *for secretion which exists in the* Mann Williamson dog (Ivy and Bachrach 1940)

Little can usefully be said of the various clinical trials which have been made of enterogastrone urogastrone and anthelone extracts (Ivy Grossman and Bachrach 1950) since it seems uncertain *whether the extracts were of satisfactory potency* and purity Such trials are in the reviewer s opinion premature until the purification of such extracts has considerably advanced

REFERENCES

Babkin B P (1928) *Die aussere Sekretionen der Verdauungsdrusen te anflage* Berlin Springer
Bauer V and Uvnas B (1944) *Acta physiol scand* 8 158
Bayliss W M and Starling E H (1902) *J Physiol* 28 325
Best C H and McHenry E W (1930) *Ibid* 70 349
Edkins J S (1906) *Ibid* 34 133
Emmelin N and Kahlson G S (1944) *Acta physiol scand* 8 89
Ewald C A and Boas J (1886) *Virchows Arch* 104 271
Farrell J I and Ivy A C (1926) *Amer J Physiol* 76 227
Feng T P Hou H C and Lim R K S (1929) *Chin J Physiol* 3 371
Gavin B McHenry E W and Wilson M J (1933) *J Physiol* 79 234
Gray J S Bradley W B and Ivy A C (1937) *Amer J Physiol* 118 463
— Wieczorowski E Wells J A and Harris S C (1942) *Endocrinology* 30 1 9
Gregory R A (1950) *Gastroenterologica Basel* 76 82
— and Ivy A C (1941) *Quart J exp Physiol* 31 111
Grindlay J H (1941) *Amer J Digest Dis* 8 82
Grossman M I (1950) *Physiol Rev* 30 33
— and Robertson C R (1948) *Amer J Physiol* 153 447
— — and Ivy A C (1948) *Ibid* 153 1
— Woolley J R and Ivy A C (1944) *Ibid* 141 506
Harper A A (1946) *J Physiol* 105 31P
Ivy A C and Bachrach W H (1940) *Ibid Dis* 7 76
— and Farrell J I (1925) *Amer J Physiol* 74 639
— and Gray J S (1937) *Cold Spr Harb Symp quant Biol* 5 405
— Grossman M I and Bachrach W H (1950) *Peptic Ulcer* p 440 London Churchill
— and Whitlow J E (1922) *Amer J Physiol* 60 578
Jemerin E E Hollander F and Weinstein V A (1943) *Gastroenterology* 1 500
Komarov S A (1938) *Proc Soc exp Biol* 38 514
Kosaka T and Lim R K S (1930) *Chin J Physiol* 4 213
Le Conte P (1900) *La Cellule* 17 285
Lim R K S Ivy A C and McCarthy J E (1925) *Quart J exp Physiol* 15 13
London E S (1913) *Physiol u Path Chymologie* p 213 Leipzig Springer
— (1925) *Exp Path u Physiol d Verdauung* p 158 Berlin Springer
Markowitz J (1949) *Textbook of Experimental Surgery* 2nd ed London Baillière
Necheles H (1945) *Gastroenterology* 5 427
Pavlov I P (1910) The Work of The Digestive Glands 2nd English Ed
Popielski L (1909) *Pflug Arch ges Physiol* 126 483
— (1913) *Ibid* 150 1
— (1920) *Ibid* 178 214
Portis S A and Portis B (1926) *J Amer Med Ass* 86 836
Quigley J P Zettleman H J and Ivy A C (1934) *Amer J Physiol* 108 643
Robertson C R Langlois K Martin C G Slezak G and Grossman M I (1950) *Ibid* 163 ~~162~~ 27
Rogers J Rahe J M Fawcett G G and Hackett G S (1916) *Ibid* 39 345
— — and Ablahadian E (1919) *Ibid* 48 79
Sacks J Ivy A C Burgess J P and Vandolah J E (1932) *Ibid* 101 331
Sandweiss D J (1945) *Gastroenterology* 5 404
Savitsch W and Zeliony G (1911) *Arch Sci biol St Petersb* 11
— — (1913) *Pflug Arch ges Physiol* 150 128
Shapiro P F and Berg B N (1934) *Arch Surg* 28 160
Smidt H (1923) *Arch klin chir* 125 26
Sokolov (1904) *Dissertation* St Petersburg Quoted by Pavlov (1910)
Uvnas B (1942) *Acta physiol scand* 4 *Suppl* 13
— (1945) *Ibid* 9 296
Wilhelmj C M O Brien F T and Hill F C (1936) *Amer J Physiol* 116 685

Section III

Assessment

J N Hunt

For many years it has been recognized that an analytical study of gastric contents can be of value in the clinical diagnosis of disorders affecting the stomach and duodenum but owing to wide variations in behaviour even between members of a group of normal persons the information obtained is not always useful

Such analyses of gastric contents should also lead to a greater understanding of the physiology of normal gastric secretion but as there has been a tendency to assess gastric secretory function directly from an analysis of gastric contents the several factors influencing the composition of the latter have often been overlooked

Recent advances in the technique of investigating the behaviour of the stomach have made possible the separate evaluation of some of the factors contributing to the acidity of the gastric contents In this section some advances of technique will first be described and then it will be shown how these methods help to separate the contributions of the several gastric functional components the activity of which is finally reflected in the composition of the gastric contents The main purpose of this section is to show how some of the differences between the gastric secretory function of different individuals may be attributed to special functional components of the gastric secretory mechanism

COLLECTION OF GASTRIC CONTENTS

Because all information about the secretory activity of the stomach in man must depend upon the results of analysis of gastric contents it is necessary to discuss some of the practical details of recovery and analysis

The liquid gastric contents may consist of (1) gastric secretion (2) saliva (3) regurgitated duodenal contents and (4) food residues

Saliva and duodenal contents may both contain bicarbonate the concentration in duodenal contents reaching 140 milliequivalents per litre (Dreiling and Hollander 1950) so that duodenal contents are sometimes potent in neutralizing the acid of the gastric secretion Saliva contains low concentrations of chloride and bicarbonate so that it is mainly a diluent and only secondarily a neutralizing agent

It is difficult to collect a sample of uncontaminated gastric secretion in man Apart from data on samples yielded by very rare persons with gastric pouches (Jamieson 1950) the best data are those of Ihre (1938) He allowed at least an hour to elapse between the swallowing of a double bore tube and starting his collections He drew up saliva duodenal contents and gastric contents separately and he used potent stimuli so that the volume of gastric secretion was large relative to the volume of contaminants When these precautions are not taken the

composition of a sample of gastric contents even in the absence of ingested food may be little related to the composition of gastric secretion a point which applies particularly to the so-called resting juice

ANALYSIS OF SPECIMENS AND EXPRESSION OF THE RESULTS

When measurements of the acidity of gastric contents are made the units in which the results are expressed should be chosen according to the purpose of the experiments and according to the acidity of the gastric contents The results of titrations of abundant free acid that is titration to *p*H 3 or 4 should be expressed in milliequivalents per litre The use of a *p*H scale masks the true magnitude of differences between readings for example *p*H 1 corresponds to 100 times the acidity of *p*H 3 Titration of total acid to *p*H 6 5 using phenol red or a *p*H meter is recommended because *p*H 6 5 is the highest isoelectric point of the gastric proteins which contribute a minimum error at this *p*H

Where small changes in the acidity of the gastric contents containing no free acid that is having a *p*H higher than 3 are in question changes should be followed with a *p*H meter If the results are expressed as a mean they should be translated from the *p*H scale to hydrogen ion concentrations Averages of *p*H values that is means of the negative logarithm of hydrogen ion concentrations have no physio logical or clinical meaning

To assess gastric secretion quantitatively a knowledge of the concentration of chloride in recovered gastric secretion is desirable for reasons which will appear later The titration of chloride by electrometric methods can now be as quick as the titration of acid (Ihre 1938)

A method of measuring peptic activity should give results which are comparable from year to year in different laboratories The method of Anson and Mirsky (1932) and Anson (1938) in which haemoglobin is digested is the most widely used and gives reproducible results but different samples of haemoglobin may give different results for the same sample of secretion This difficulty has been overcome by substituting dried plasma or serum proteins for haemoglobin Serum or plasma whether prepared in England or the United States of America gives results which do not usually differ by more that 3 per cent from sample to sample of protein (Hunt 1948a) Plasma proteins have another advantage in that the results of the measurement of peptic activity do not depend upon the dilution of the sample as they do with haemoglobin (Hunt 1948b) Thus the use of plasma proteins provides results which are truly comparable between different laboratories

INORGANIC CONSTITUENTS OF GASTRIC SECRETION

In the past the results of experiments on gastric secretion have often been expressed as the acidity and volume of the secretion However it is now possible to describe a secretory response in terms of the volumes of two separate secretions from the gastric mucosa which mix in the stomach to form the gastric juice This simplifies the interpretation of the results

Hollander (1938) suggested that the inorganic substances of the gastric secretion of dogs had their origin in two components The composition of the two com ponents was fixed and did not alter but where the acidity of the total gastric

SECTION III

ASSESSMENT

J N HUNT

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The liquid gastric contents may consist of (1) gastric secretion (2) saliva (3) regurgitated duodenal contents and (4) food residues

Saliva and duodenal contents may both contain bicarbonate the concentration in duodenal contents reaching 140 milliequivalents per litre (Dreiling and Hollander 1950) *so that duodenal contents are sometimes potent in neutralizing* the acid of the gastric secretion Saliva contains low concentrations of chloride and bicarbonate so that it is mainly a diluent and only secondarily a neutralizing *agent*

It is difficult to collect a sample of uncontaminated gastric secretion in man Apart from data on samples yielded by very rare persons with gastric pouches (Jamieson 1950) the best data are those of Ihre (1938) He allowed at least an hour to elapse between the swallowing of a double bore tube and starting his collections He drew up saliva duodenal contents and gastric contents separately and he used potent stimuli so that the volume of gastric secretion was large relative to the volume of contaminants When these precautions are not taken the

from the usual interpretation of such a finding namely that no acid had be n secreted

PEPSIN IN GASTRIC CONTENTS

The interpretation of data on amount of pepsin recovered from the stomach presents a special difficulty If the stomach is washed out before an experiment is begun the amount of acid formed during the experiment clearly represents the work of the parietal cells in that period for we have no evidence that acid is stored in the mucosa However the output of pepsin during an experimental period is more than the pepsin extruded from the pepsin secreting cells during that period A considerable quantity of pepsin may lie pre formed in the gastric tubules ready to be flushed out by fluid of the gastric secretion produced under the influence of such a stimulus as histamine which probably does not stimulate the pepsin producing cells Thus the output of pepsin following a stimulus to the pepsin producing cells which is usually of necessity a stimulus to the parietal cells consists of washed out pepsin plus pepsin truly secreted that is pepsin extruded from the pepsin producing cells under the influence of the stimulus Thus if interest is focused on the measurement of the power of a stimulus to activate the pepsin secreting cells the gastric tubules ought first to be flushed out by the use of some stimulus such as histamine a procedure adopted by Ihre (1938) when he gave successive histamine and insulin tests The pepsin producing cells contribute a negligible amount of fluid to the gastric secretion

INTERPRETATION OF TEST MEAL RESULTS

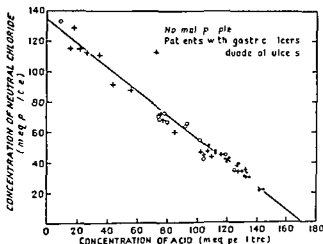
As now used the fractional test meal method can give information about the concentrations of acid chloride and pepsin in the gastric contents and allows an assessment of the environment offered to the external surface of the gastric and duodenal mucosa Test meals give data for comparison within an individual and between individuals only in respect of their gastric contents However there are many workers who have not found this limitation acceptable and have supposed that the acidity of the gastric contents has a direct be ring on the amount of acid secreted by the stomach The acidity of the gastric contents is merely the ratio of the amount of acid that is hydrogen ions in the stomach to the volume of the gastric contents Expressed in this way it is cle r that the acidity is the resultant of the interplay between gastric emptying and secretion and therefore no separate conclusions can be drawn either about emptying or about secretion from the acidity of the gastric contents This inescap ible conclusion h s been pointed out by a number of authors but neglected by a far larger number One cause of this refusal to face an obvious limitation of the fractional test me il method was the lack of any reliable way of measuring the volume of gastric secretion in response to a test meal Recently this has been remedied by the development of the Serial Test meal technique (Hunt and Spurrell 1951 Hunt 1951)

The Serial Test meal involves giving a stand ird meal to a subject on successive days and withdrawing the whole of the gastric contents after progressively longer periods on each occasion From the volume of the gastric contents and the con centrations of acid chloride and pepsin the tot il amounts of these constituents in the stomach after various digestive periods may be found The inclusion of a

secretion varied this variation was the result of different proportions of the two components

The compositions of these two components of human gastric juice have been suggested by Fisher and Hunt (1950) using the results of Ihre (1938) It was found that the acid or parietal component contained 160 milliequivalents per litre The alkaline or non parietal component contained 45 milliequivalents of acid p r litre of bicarbonate and 125 milliequivalents per litre of so called neutral chloride that is chloride ions in electrical equilibrium with sodium and potassium ions

If two solutions of the same compositions as those of the suggested components of gastric secretion were mixed in varying proportions analysis of the mixtures would give points precisely on the straight line of Fig 102 in which concentrations of neutral chloride in samples of the mixture have been plotted against concentrations of acid The points plotted from Ihre s data on human gastric secretion including that from patients with peptic ulcers fall very close to this line in Fig 102



Fic 102 —Concentration of acid plotted against concentration of neutral chloride in gastric juices secreted during hypoglycaemia (Ihre 1938) (*Bi courtesv of Lancet*)

Thus the two component hypothesis accounts quantitatively for Ihre s observations on the composition of human gastric secretion On the basis of this hypothesis it is possible to calculate from the amounts of acid and chloride recovered from the stomach the volumes of the two components which have been secreted Given the volume and the acidity of a sample of gastric contents it is possible to divide it into its constituent volumes of the two components

From the two component hypothesis it follows that the amount of acid in a sample of gastric secretion is not equal to the amount secreted and when the acidity of the sample is low the difference between the amount of acid secreted and the amount recovered may be considerable The bicarbonate-containing secretion referred to as the alkaline or non parietal secretion neutralizes the acid component when the two mix in the stomach In fact 3 5 litres of alkaline secretion neutralize 1 litre of acid component Thus if 4 5 litres of neutral gastric juice were to be withdrawn from the stomach it could be inferred that 1 litre of acid secretion had been formed and neutralized in the stomach Thi is quite different

in use It has the advantage over gruel meals that it would be possible to produce the same standard meal in any laboratory

The pectin meal is slightly fruity bland and certainly not sufficiently palatable to arouse appetite It was made so by design in order to eliminate as far as possible wide variations in the psychic response to it It contains nothing which is known to stimulate gastric secretion chemically and it is therefore presumed that it stimulates only by distension

RATE OF SECRETION OF GASTRIC JUICE

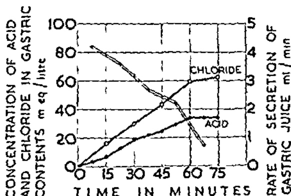


FIG 105 —Rate of secretion of gastric juice and concentration of acid and chloride in the gastric contents with the pectin test meal (Means for 19 subjects)

The Serial Test meal has been used in a study of 19 normal subjects The results of the secretory studies are set out in Fig 103 which shows the mean volume and acidity of the gastric juice secreted in response to 750 millilitres of pectin meal It may be seen that the maximum rate of secretion is reached within the first 15 minutes of the digestive period and after that it progressively declines Fig 104 shows that the output of pepsin in response to the meal also falls off as the digestive period progresses In Fig 105 the concentration of acid and chloride in the gastric contents has been plotted on the same graph as the rate of secretion of the gastric juice It may be seen that the uniform rate of increase in the concentration of acid in the gastric contents is produced by a continuously declining rate of secretion a fact which is explained by the continuous reduction in the total volume of gastric contents and the decreasing acidity of the gastric secretion Clearly there can be no measurements of the amounts secreted in response to a test meal without a simultaneous study of gastric emptying

MECHANISM OF CONTROL

When the stomach secretes in response to normal stimuli the process may be described in terms of the activity of a number of reflex arcs Classically the reflex arc has been divided into a receptor which is sensitive to a specific stimulus a nervous connecting link which conducts the impulses set up in the receptor to the effector organ and the effector This description is usually applied only to reflex arcs in which the process of conduction between the receptor and effector is entirely nervous but the divisions are equally applicable to an arc in which the conduction between receptor and effector is hormonal These parts of the reflex arc are as exemplified in the stomach shown in Fig 106

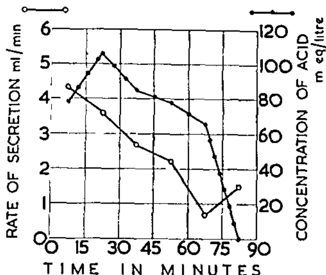


FIG 103 —Rate of secretion of gastric juice and concentration of acid in gastric juice with the pectin test meal (Means for 19 subjects) (*By courtesy of Journal of Physiology*)

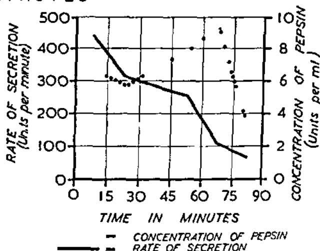


FIG 104 —Rate of secretion of pepsin and concentration of pepsin in gastric secretion in response to pectin test meal (Means for 19 subjects) (*By courtesy of Journal of Physiology*)

non absorbable dye in the meal allows the volume of the gastric contents passing into the duodenum to be calculated With this information and a knowledge of the mean concentrations of acid chloride and pepsin in the gastric contents it is *possible to compute the amounts of these constituents leaving the stomach* Knowing the amount of acid in the stomach and the amount that has left by the pylorus it is possible to calculate the total amount of acid secreted A similar calculation may be made for chloride and pepsin The results may then be trans formed into volumes of parietal and non parietal secretion (Fisher and Hunt 1950) Alternatively the results may equally well be expressed as the volume and acidity of the gastric secretion

To use the Serial Test meal technique it was necessary to have a meal which could be accurately and easily standardized and which allowed the estimation of the dye included in the meal A meal containing pectin and sucrose with a fixed viscosity osmotic pressure and pH was devised and has proved quite satisfactory

The results of giving a standard stimulus to a number of such arcs with different characteristics will be considered first Fig 106 shows what may be considered a normal arc The application of a standard stimulus to such an arc can be supposed to lead to the discharge of a single impulse from the receptor along the connector causing the stomach to produce one unit of secretion This may be described as the normal secretory response

In Fig 107 is shown an arc in which the receptor is twice as sensitive or reactive as that of the normal arc the other parts being precisely the same as in Fig 106

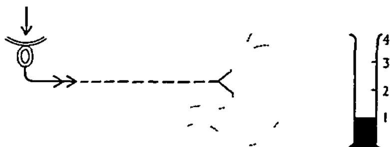


FIG 110—An arc with a doubly reactive receptor and a half reactive effector

The doubly sensitive receptor represented in Fig 107 in double lines will give rise to 2 impulses in response to the standard stimulus these are shown on the connector as 2 arrows instead of the 1 arrow on the connector in Fig 106 These 2 impulses when they reach the stomach will give rise to 2 units of secretion This is clearly one possible cause of hypersecretion in response to a standard stimulus

An arc in which the receptor is normal but the effector organ is doubly reactive is shown in Fig 108 by drawing the stomach in double lines In such an arc 1 single impulse represented by 1 arrow on the connector will evoke 2 units of secretion This is a second possible cause for hypersecretion in response to a standard stimulus applied to the receptor

Fig 109 shows an arc with a doubly reactive receptor connected to a doubly reactive effector In such an arc the standard stimulus will give rise to 4 units of secretion instead of the normal 1 unit

Fig 110 shows an arc in which the doubly reactive receptor is connected to a half reactive effector shown in the figure by drawing the stomach in dotted lines The application of the standard stimulus to such an arc will give rise to a normal 1 unit of secretion Such a normal result clearly does not allow the conclusion that the whole mechanism of the arc is normally reactive

Since it is not yet practical to assess the reactivity of the receptors and connectors separately the complications introduced by a separate consideration of these parts will be passed over in the discussion which follows

INTERPRETATION OF RESULTS OF THE HISTAMINE TEST

It is known that the stomach of man responds to many kinds of stimuli for example a meal hypoglycaemia and even basal conditions are all associated with secretion This is shown in Fig 111 The responses to these stimuli have one factor

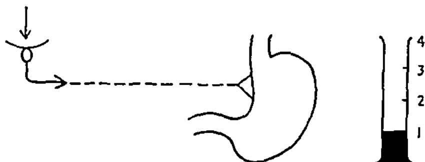


FIG 106 —A normal arc

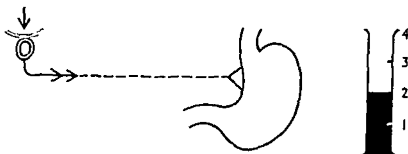


FIG 107 —An arc with a doubly sensitive receptor

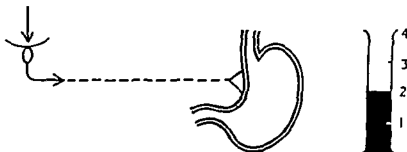


FIG 108 —An arc with a doubly reactive effector

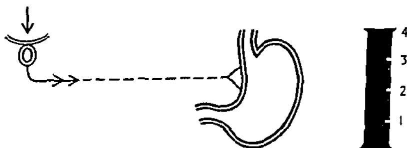


FIG 109 —An arc with doubly reactive receptor and doubly reactive effector

stomach of Fig 106 gives 1 unit of secretion in response to a standard dose of histamine and gives 1 unit of secretion in response to a standard meal the response to a meal divided by the response to histamine that is $\frac{M}{H}$ gives the answer 1 indicating a normally reactive receptor connector unit In the conditions of Fig 107 the $\frac{M}{H}$ ratio will be 2 indicating that the receptor-connector unit is doubly reactive Under the conditions of Fig 108 the standard dose of histamine will evoke 2 units of secretion as will the standard meal the $\frac{M}{H}$ ratio will therefore be 1 Thus the $\frac{M}{H}$ ratio is an index of the reactivity of the receptor connector unit responding to the meal quite independent of the reactivity of the gastric secretory cells A further consideration of the use of histamine in this way has been published elsewhere (Hunt 1950a)

SIGNIFICANCE OF HISTAMINE TEST IN PATIENTS WITH PEPTIC ULCERS

The type of analysis described above has been used to find out whether patients with peptic ulcers have any abnormality of the receptor-connector units which respond to hypoglycaemia when this causes gastric secretion An analysis of Ihre s (1938) data showed that male patients with duodenal ulcers secreted a mean of 146 millilitres of acid component as compared with 103 millilitres secreted by normal subjects when both groups were given equal doses of insulin Was this extra secretion obtained from the patients with duodenal ulcers the result of their receptors being extra sensitive to the hypoglycaemia caused by the insulin or was it the result of their parietal cells being extra reactive to the stimulation reaching them? In response to histamine the same group of Ihre s patients with duodenal ulcers secreted a mean of 120 millilitres of parietal component as compared with 92 millilitres of parietal component secreted by the group of normal subjects Dividing the response to insulin by the response to histamine gives precisely the same $\frac{I}{H}$ ratio for each group This suggests that the hypersecretion in response to insulin given to patients with duodenal ulcer was the result of hyper reactive effector parietal cells and was not the result of the receptors responding to hypoglycaemia being over reactive

The data for patients with gastric ulcers showed that both their receptors and their effectors that is the parietal cells were normally reactive

The secretion of pepsin in response to hypoglycaemia in Ihre s patients was comparable with the secretion of the parietal component Patients with duodenal ulcers secreted nearly twice as much pepsin as normal subjects in response to insulin This was entirely the result of the hyper reactivity of the pepsin secreting cells and was not due to hyper reactive receptors responding to hypoglycaemia The peptic response of patients with gastric ulcers is similar to that of normal subjects

Thus in patients with duodenal ulcers the cells secreting acid and pepsin seem to be hyper reactive The cause of this hyper reactivity is not known but it is reduced after vagotomy after cutting the vagi in patients with peptic ulcer the

in common they all involve the secretory action of the stomach Thus other things being equal if the reactivity of a person s stomach is low there will be a tendency for the gastric responses of that person to standard stimuli of all types to be low if the reactivity of the stomach is high there will be a tendency for the responses to standard stimuli to be high

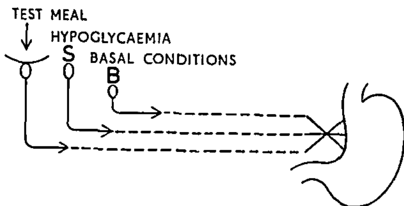


FIG 111 —Three secretory gastric reflex arcs

It would be useful if there were some way of assessing the reactivity of the secretory mechanism of the stomach to the impulses arriving *via* the normal connector pathways To do this a stimulus which acts *directly on the stomach* must be used thus avoiding differences between subjects due to variations in the receptors and connectors playing on the stomach Histamine is a substance which acts directly on the stomach since it is effective after the extrinsic nerves have been cut and it is conceivable that it could serve as such a stimulus However before the response to histamine can be used to assess the reactivity of the stomach to normal stimuli it is necessary to inquire if the response to histamine does in fact vary with the responses to stimuli arriving *via* the normal connectors

This point was examined in the following way A group of normal subjects was given a standard dose of histamine and the amount of parietal component secreted was recorded The same subjects were then given a Serial Test meal and the output of parietal secretion was recorded The response to histamine was then plotted against the response to the pectin test meal It was found that persons who had large responses to the test meal had large responses to histamine those with small responses to the test meal had small responses to histamine Data for the secretion of parietal component in response to histamine and basal conditions and histamine and insulin induced hypoglycaemia were similarly examined From each of these plots it was clear that the greater the response of the subjects to histamine the greater was their response to the other stimuli These findings made it reasonable to use the response to histamine as an index of the reactivity of the parietal cells to normal stimuli Similar examinations of data for the alkaline non parietal component and for pepsin led to the conclusion that histamine might also be used to test the reactivity of the cells secreting these constituents of the gastric juice

A few examples of the use of histamine to assess reactivity follow The normal

results are transformed into volumes of parietal and non parietal component errors which are almost inevitable *will tend to give values for the parietal* component which are too small and values for the non parietal component correspondingly too large From the results of Levin Kirsner Palmer and Butler (1948) and Woodward Harper Tovee and Dragstedt (1949) it was found that the mean volume of parietal component recovered from normal male persons during 12 hours nocturnal aspiration was 240 millilitres (standard error of mean ± 22 millilitres) A group of male patients with duodenal ulcers yielded a mean of 525 millilitres (standard error of mean ± 29 millilitres) that is twice as much as the group of normal persons It has been suggested that the increased secretion in patients with duodenal ulcers is caused by a persistent psychic phase of secretion The finding that the nocturnal basal secretion is greatly reduced by a section of the vagus nerves which carry the impulses of the psychic phase of secretion is compatible with this view but there is an alternative The stomachs of patients with duodenal ulcers are hyper reactive to histamine so that it would be expected that they would hypersecrete in response to all stimuli whether the stimulation came *via* nervous or humoral channels This hyper reactivity depends upon the integrity of the vagus for the parietal response to histamine is reduced by vagotomy Thus vagotomy would be expected to reduce the parietal response to all kinds of stimulation nervous or hormonal It follows therefore that the reduction in basal nocturnal secretion after vagotomy cannot be used as evidence that the secretion is the result of secretory impulses passing down the vagus nerves When this question was considered quantitatively it was found that vagotomy reduced the mean parietal response to histamine from 185 to 47 millilitres that is by 75 per cent (Oberhelman and Dragstedt 1948) Thus no matter what was the cause of the basal nocturnal parietal secretion it would be expected *that vagotomy would reduce it by 75 per cent In fact Oberhelman and Dragstedt s* figures show that the basal nocturnal secretion of parietal component was reduced by vagotomy from a mean of 525 to 170 millilitres that is by 70 per cent If the vagus had contained two sets of fibres one carrying impulses maintaining the reactivity of the parietal cells and another carrying secretory impulses responsible for part of the basal nocturnal secretion section of both sets would be expected to decrease the basal nocturnal secretion by more than 75 per cent As this did not occur it is possible to argue that secretory impulses passing down the vagus are not responsible for the basal nocturnal secretion of the parietal component in patients with duodenal ulcers

An analysis on these lines of the data in the literature on nocturnal secretion is at present in progress in this laboratory So far the results suggest that a raised basal nocturnal secretion can best be accounted for on the basis of a raised peripheral reactivity

CONCLUSIONS

From data which have been examined it appears that the major portion of the differences between the gastric secretory responses of persons to standard stimuli can be attributed to differences in gastric reactivity as assessed with histamine This is comparable to saying that the variations between different persons in the

response of the parietal cells to histamine was reduced to about 25 per cent of its pre operative value (Oberhelman and Dragstedt 1948) The recent findings of Gray Spiro and Reifenstein (1950) that adrenal cortical hormones augment the gastric secretion of pepsin may be relevant in this connection

In patients with gastric ulcers and in patients with duodenal ulcers the secretion of alkaline non parietal component in response to hypoglycaemia was twice as great as in normal subjects In patients with duodenal ulcers the hypersecretion of the alkaline component in response to hypoglycaemia was the result of hyper reactivity of the secretory effector cells The receptors were apparently normally reactive On the other hand in patients with gastric ulcers there was in addition a hyper reactivity of the receptor connector unit of the reflex arc which responds to hypoglycaemia The finding of a hyper reactivity of the receptors responding to hypoglycaemia in patients with gastric ulcers which is not present in patients with duodenal ulcers is yet one more distinction between these two conditions The analysis summarized above is given in more detail elsewhere (Hunt 1950b)

There is no proof that the receptors and connectors activated by hypoglycaemia are involved in the normal regulation of the secretion of the alkaline component but it is perhaps worth recalling the work of James and Pickering (1949) in this context These authors noted that patients with gastric ulcers frequently had neutral gastric contents during the night whilst the gastric contents of normal persons and patients with duodenal ulcers rarely reached neutrality The evidence of James and Pickering would be compatible with a hypersecretion of the alkaline component during the night in patients with gastric ulcers as compared with the other two groups a finding which might be linked to the hyper reactivity of the receptor connector system Alternatively their results can be explained on the basis of patients with gastric ulcers secreting less acid than normal subjects during the night

ORIGIN OF VARIATIONS IN SECRETORY RESPONSE TO THE PECTIN MEAL

The data on subjects who were given both pectin meals and histamine tests showed that the scatters about the mean parietal responses for the two tests were equal This finding at first suggests that variations in the gastric mucosae in different subjects as tested with histamine are as large as the variations in the more complex receptor connector effector units which respond to the pectin meal This would imply that there was no variation between individuals in the receptor connector units which seems an untenable hypothesis Further consideration of the data showed that the greater was a person s response to histamine the smaller the fraction of the gastric secretory capacity as assessed with histamine which was used in the response to the pectin meal It seems possible that this state of affairs could be accounted for by an inhibitory mechanism coming into play when the acidity of the gastric contents rises above a certain level which would tend to limit variations between individuals in the amounts of acid secreted in response to the pectin test meal

SIGNIFICANCE OF BASAL NOCTURNAL SECRETION

The results of collections of nocturnal secretion are usually expressed in terms of the volume of secretion and the amount of acid collected in 12 hours When these

CHAPTER 13

THE VASCULAR ANATOMY OF THE STOMACH

F H BENTLEY AND T E BARLOW

THE course and general distribution of the arteries and veins of the stomach are well known On the lesser curvature of the stomach run the right and left gastric vessels and on the greater curvature is the gastro epiploic chain consisting of right and left gastro-epiploic arteries and veins reinforced at the left extremity by the vasa brevia

The left gastric artery usually divides into two main channels one running on the anterior and the other on the posterior aspect of the lesser curvature both vessels lying within the limits of the lesser omentum As a rule the anterior branch (but sometimes both branches) joins directly with the right gastric artery

The distribution of these main vessels within the stomach wall is less generally understood and is the subject of this account It varies in different parts of the stomach but the anterior and posterior walls of the body of the stomach have a precisely similar vascular arrangement and will be first described

THE ANTERIOR AND POSTERIOR WALLS OF THE BODY OF THE STOMACH

The submucous plexus

These areas of stomach wall are supplied by branches from the arterial chains on both greater and lesser curvatures Those from the left gastric artery arise at intervals of about one centimetre along its length and pass obliquely across the stomach inclining towards the pylorus and pierce the muscle coat 1–2 centimetres from the lesser curve to reach the submucous layer of the stomach wall As the vessels traverse the muscle they give off small branches to supply it In the sub mucosa they join with comparable branches from the gastro epiploic chain to form a large plexus (Fig 112)

The main channels of this submucous plexus consist of vessels about 200 microns in diameter in the fixed specimen the large limbs of the plexus being further con nected by smaller branches about 150 microns in cross section which lie a little deeper in the submucous connective tissue (Fig 113) The extensive vascular network is continuous over the anterior and posterior walls and gives origin to the arteries supplying the mucous membrane

The mucosal branches

Arteries destined for the supply of the mucosa arise from the main and subsidiary communicating channels of the submucous plexus They are about 100–120 microns in diameter and pass obliquely through the submucous connective tissue towards the muscularis mucosae As a mucosal artery approaches this muscular tissue it breaks up into 2–3 smaller branches which often twist and coil around each

force which can be exerted by flexing the forearm can be mainly attributed to variations in the mass of muscle moving the forearm

SUMMARY

In this section the following distinctions have been made

(1) Gastric secretion has been distinguished from extra gastric contaminants

(2) The hypothetical acid parietal component has been distinguished from the hypothetical alkaline non parietal component

(3) The contributions of emptying and secretion to the acidity of the gastric contents after a test meal have been discussed and attention has been called to a practical method of assessing these contributions separately

(4) The contribution of the receptor connector units and the effectors as parts of a reflex arc have been considered and a method of separating them in practice by the use of histamine has been proposed and applied to patients with peptic ulcers This approach revealed hyper reactivity of the cells secreting parietal component, non parietal component and pepsin in patients with duodenal ulcers In patients with gastric ulcers the hyper reactivity in the peripheral effectors was confined to the cells secreting the non parietal com ponent In addition in patients with gastric ulcers there was hyper reactivity of the receptors and connectors mediating the production of non parietal secretion in response to hypoglycaemia

(5) The variation in the parietal secretory response to pectin meals has been considered

(6) The possible causes of the hypersecretion of acid during the night in patients with duodenal ulcers have been examined

(7) Differences between individuals in their gastric secretory response to basal conditions hypoglycaemia and a pectin meal have been attributed mainly to variations in the reactivity of the gastric secretory cells

REFERENCES

Anson M L (1938) *J gen Physiol* 22 79
— and Mirsky A E (1932) *Ibid* 16 59
Dreiling D A and Hollander F (1950) *Gastroenterology* 15 620
Fisher R B and Hunt J N (1950) *J Physiol* 111 138
Gray S J Spiro H M and Reifenstein R W (1950) *Bull New Engl med Center* 12 169
Hollander F (1938) *J biol Chem* 125 161
Hunt J N (1948a) *Biochem J* 42 104
— (1948b) *J Physiol* 107 365
— (1950a) *Gastroenterology* 16 231
— (1950b) *Lancet* 2 397
— (1951) *J Physiol* 113 169
— and Spurrell W R (1951) *Ibid* 113 157
Ihre B (1938) *Act med scand Suppl No* 95
James A H and Pickering G W (1949) *Clin Sci* 8 181
Jamieson R A (1950) *Rev Gastroent* 17 49
Levin E Kirsner J B Palmer W L and Butler C (1948) *Arch Surg Chicago* 56 345
Oberhelman H A Jun and Dragstedt L R (1948) *Proc Soc exp Biol N Y* 67 336
Woodward E R Harper P V Tovee B B and Dragstedt L R (1949) *Arch Surg Chicago* 59 1191

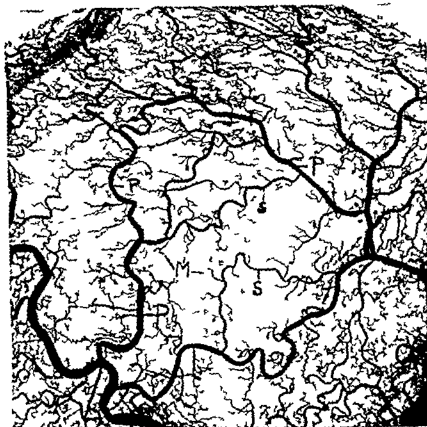


Fig. 113 – Radiograph of the submucous plexus of the anterior wall injected with gold chloride and showing main (P) and subsidiary (S) anastomotic vessels. Mucosal arteries (M) are seen arising from these vessels × 4.5

branches a vast plexus of fine vessels from capillary size up to about 60–100 microns in diameter the function of which it is difficult to conjecture. The vessels are paired artery and vein running side by side the artery usually being the smaller of the two. These vessels occupy the interstices between the limbs of the submucous plexus and are arranged in loops freely communicating with each other and with the submucous plexus from which they arise. The loops continue throughout the thickness of the submucosa as many as six different loops sometimes being visible at different depths in one microscopic field (Figs 121–123). The venous channels are notable for the presence of many small dilatations especially at the bends of the loops and at points of junction with other veins (Fig 121).

The vessels of this extensive fine plexus are in communication with vessels in the muscle wall but do not appear to join with the mucosal arteries and veins; they are expended entirely in a complicated network in the connective tissue layer of the stomach wall and do not penetrate the muscularis mucosae to reach the

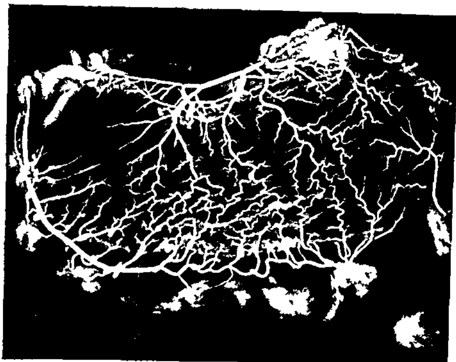


FIG 112 —Radiograph of whole anterior wall of stomach Arteries filled with 20 per cent chlorbismol The vascular chains on the greater and lesser curvatures and the plexus of vessels in the submucosa are shown × 0 4

other before separating and piercing the muscularis mucosae in an oblique direction (Figs 114 and 115) In this region just under the muscularis mucosae the mucosal *arteries or their branches are linked by slender anastomosing channels (50 microns)* each with its neighbour or sometimes with a branch a little distance away (Fig 116)

Having pierced the muscularis mucosae the mucosal branches form an anastomosing channel on its mucosal aspect and then split up into leashes of capillaries about 10 microns in diameter which run in striking fashion towards the surface (Figs 115 117 and 118) appearing almost to fill the substance of the mucosa and ramifying among the glands like the arborizations of a tree each spread of branches joining at its tips with adjacent capillary twigs and forming at the surface large capillary loops surrounding the openings of the glands (Fig 119)

The vascular arrangement thus consists of a rich mucosal supply which between its origin from the arterial chains along the stomach curvatures and its destination *in the mucosa freely anastomoses at different levels* first in the submucous plexus then between the mucosal arteries underneath the muscularis mucosae once again between the branches of the mucosal arteries on the glandular aspect of that muscle layer and finally between the capillary terminations in the mucosa (Fig 120)

The connective tissue plexus

There is a thick submucous connective tissue layer in the anterior and posterior walls and it contains in addition to the submucosal plexus and its mucosal

but pass on towards the muscularis mucosae dividing as they reach it into smaller vessels which twist around each other before passing through that muscle layer They are in fact just like the mucosal branches in the anterior and posterior walls of the stomach except that they have their origin not from a submucous plexus in the stomach wall but directly from the left gastric vessels outside the stomach and so have to pierce the muscle coat of the stomach on their long passage from origin to distribution (Fig 125)



Fig 115 —Preparation similar to Fig 114 showing a fold of mucosa P submucous plexus vessels M M M mucosal arteries showing characteristic twisting and coiling as they approach the muscularis mucosae × 17

mucosa As they lie adjacent to the main channels of the submucous plexus they are clustered about the large arteries and veins running generally parallel to them but sending many cross branches both arterial and venous in front of and behind

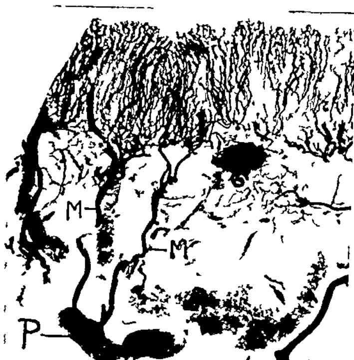


FIG 114—Radiograph of transverse section (400 microns) of *stomach wall injected with 10 per cent silver iodide showing* vessel of submucous plexus (P) with mucosal arteries (M and M) arising from it and crossing the submucous connective tissue to reach the submucosa × 16

the big vessels (Fig 124) The extent and density of the plexus suggest that it must have functions other than that of supplying the connective tissue of the submucosa

THE REGION OF THE LESSER CURVE AND THE PYLORUS

Lesser curve

The arrangement of blood vessels in this part of the stomach wall shows certain differences compared with that in the anterior and posterior walls The manner in which the vessels destined for the anterior and posterior walls leave the left gastric chain has already been described these branches piercing the muscular coat of the stomach 1–2 centimetres from the line of the lesser curve The tissue along the lesser curve and for 1–2 centimetres on either side of it is supplied by other vessels slender branches 60–100 microns in diameter which spring from the left gastric arteries and pierce the muscle coat to reach the submucosa (Fig 125) There are occasional anastomosing branches between these arteries before they penetrate the muscle coat In the submucosa the fine vessels do not form a submucous plexus



FIG 118—Preparation similar to Fig 117 Three branches (B B B) of mucosal arteries pierce the muscularis mucosae and form an anastomotic channel (D) on the mucosal aspect of the muscularis mucosae × 110

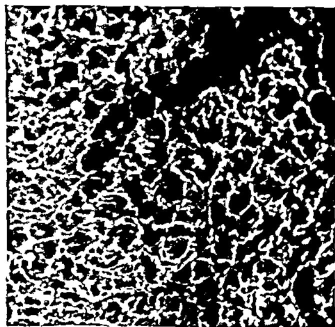


FIG 119—Radiograph of surface view of gastric mucosa vessels injected with silver iodide Note the capillary loops surrounding the openings of the glands 1?0



Fig 116—Black and white print from a coloured transparency of a specimen in which arteries and veins are injected with coloured dyes M and M are two *mucosal arteries* A is the anastomotic channel connecting them on the proximal (or under) side of the muscularis mucosae Note the large size of the accompanying veins × 31

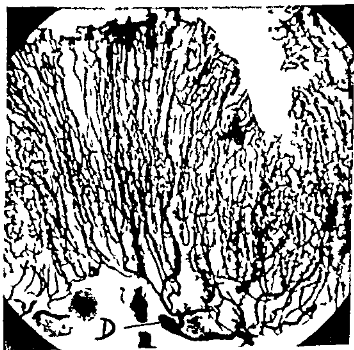


Fig 117—Black and white photograph of mucosal capillaries injected with coloured dye Note an anastomotic channel (D) on the distal (or mucosal) side *of the muscularis* mucosae and the extensive capillary ramifications × 14 5



FIG 118 —Preparation similar to Fig 117 Three branches (B B B) of mucosal arteries pierce the muscularis mucosae and form an anastomotic channel (D) on the mucosal aspect of the muscularis mucosae × 110

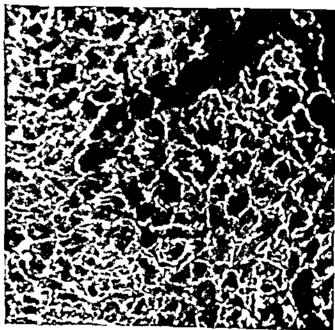


FIG 119 —Radiograph of surface view of gastric mucosa vessels injected with silver iodide Note the capillary loops surrounding the openings of the glands × 1.0

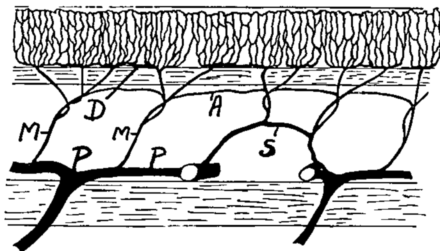


FIG 120 Diagram of vascular arrangement in the anterior and posterior walls P submucous plexus S subsidiary anastomosis M mucosal artery A D anastomotic branches connecting mucosal arteries proximal (A) and distal (D) to the muscularis mucosae

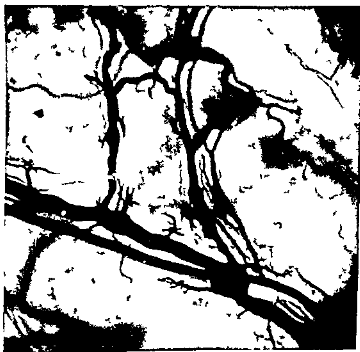


FIG 121 —Black and white print of a coloured transparency showing loop of connective tissue plexus artery (grey) and vein (black) Note the venous dilatations 35



FIG 122 —Preparation as in Fig 1 1 showing loops of the connective tissue plexus A limb of the submucous plexus (P) and a mucosal branch (M) can be seen in the background × 35



FIG 123 —Preparation as in Fig 121 Further loops of the connective tissue plexus This field shows the presence of a number of loops in depth × 35



FIG 124 —Black and white photograph of a portion of submucous plexus injected with indian ink Note artery (P) and veins (V) of submucous plexus with vessels of the connective tissue plexus running alongside and sending cross branches in front of and behind the main channels × 30

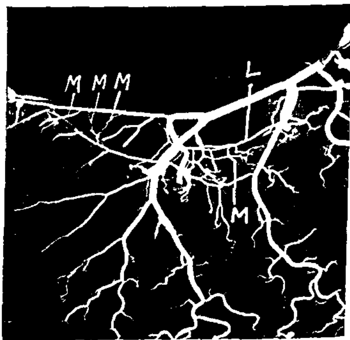


FIG 125 —Lesser curve region enlarged from Fig 112 Note mucosal arteries of lesser curve (M M M) arising from left gastric chain outside the stomach wall *L* anastomotic branch outside the muscle wall from which *further mucosal* branches (M) are arising × 0 8

Fig 126—Diagram illustrating the origin of mucosal arteries in the lesser curve and in the anterior and posterior walls P submucous plexus M mucosal artery L L left gastric arteries



Fig 127—Black and white photograph of arteries in the submucosa of the pyloric region injected with coloured dye C cut ends of arteries as they reach the submucosa S anastomotic channels M mucosal arteries Compare anastomosing channels (S) with the subsidiary anastomosis (S) of Fi 113 2 5

The mucosal arteries are distributed to the mucous membrane in a precisely similar manner to the mucosal vessels in the anterior and posterior walls as they approach the muscularis mucosae they anastomose with each other or where the lesser curve merges with the anterior and posterior walls with the corresponding mucosal artery from the submucous plexus of those regions Having pierced the *muscularis mucosae they form* an anastomosing channel on its mucosal aspect before splitting up into arborizing capillary vessels characteristic of the gastric mucosa

Pyloric region

As the stomach narrows into the pyloric canal the large submucous plexus of the anterior and posterior walls becomes less evident Branches from the right gastric and right gastro epiploic arteries spread across the outer surface of the muscle coats and break up into smaller branches which pierce the muscle obliquely On reaching the submucosa these vessels divide again into 3–4 slender arteries 100–150 microns in diameter which pass obliquely across the submucosa and end by anastomosing with similar branches of neighbouring arteries (Fig 127) These vessels are comparable in size to those smaller cross anastomotic channels between the main limbs of the submucous plexus in the anterior and posterior walls The mucosal arteries arise from these slender vessels and have the routine distribution and arrangement of such arteries elsewhere in the stomach anastomosing as they approach the muscularis mucosae and supplying the mucosa in the usual manner

The connective tissue plexus

The submucous connective tissue layer in the lesser curve and pyloric regions is thinner than in the anterior and posterior walls and contains a less extensive plexus of vessels with fewer arterial and venous loops The plexus nevertheless forms a complicated network surrounding and crossing the main channels of the mucosal supply in a manner generally similar to that seen in the walls of the body *of the stomach*

THE VENOUS DRAINAGE

Only in the mucous membrane does the venous drainage of the stomach wall differ from the arterial pattern *Blood from the surface capillaries of the mucosa is* collected into large venules 60–90 microns in diameter which lie very close to the surface (Fig 128) Several of these collecting venules join to form a mucosal vein which runs vertically through the mucosa and pierces the muscularis mucosae to enter one *of the large venous channels which accompany the mucosal arteries there* From thence onwards the course is similar to that of the arteries The notable features of the venous drainage are first the presence of relatively large veins *immediately beneath the surface of the mucosa* and *secondly* the large calibre of the veins in the submucosa (Fig 116)

ARTERIOVENOUS ANASTOMOSES

Direct arteriovenous communications are present in the stomach wall uniting arteries and veins by channels which at no point in their course are less than 30 microns in diameter in the fixed specimen and which in the living tissue can



(a) Coloured print of an arteriovenous anastomosis in the submucosa injected with coloured dyes (artery red vein blue) An arterial and a venous limb of the submucous plexus cross the centre of the field Arising from the artery is a tortuous vessel which passes towards the top of the field where it joins directly with a channel which bends underneath it to reach the submucous vein × 30



(b) Coloured print of an arteriovenous anastomotic loop in the submucosa (artery red vein blue) The continuous channel between mucosal artery and vein can be readily followed × 40

PLATE VI

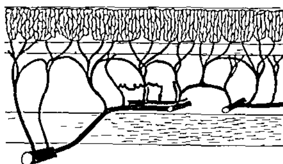


Diagram of the gastric blood supply On the extreme left is shown the arrangement in the lesser curve the mucosal arteries arising outside the stomach On the right is the arrangement in anterior and posterior walls In the centre is an arteriovenous anastomosis in relation to a mucosal artery

transmit glass spheres up to 140 microns in diameter (Walder 1950) The arterial end of the anastomotic channel usually springs from a mucosal artery or one of its branches and frequently exhibits several sinuous bends as it traverses the submucosa After a fairly long course it narrows and joins a vein which quickly widens again into a short tributary draining into a mucosal vein or directly into a vein of the submucous plexus (Plate V(*a*))

These arteriovenous communications are all simple direct channels the complicated knot of vessels (glomus) often described in arteriovenous anastomoses has not been observed by us in the human stomach They do however show considerable variation in length and direction In most instances the sinuous



FIG 1 8—Black and white print from a coloured transparency of a specimen injected with coloured dyes Note large collecting venules close to the surface and vertical channels through mucosa to the submucous vein (V) × 37 5

arterial part of the anastomotic vessel wanders across the submucosa close to and sometimes in the muscularis mucosae before emptying into a mucosal vein Sometimes the course is short the small artery doubling back on itself to end in the vein corresponding to the artery from which it is derived A not uncommon junction forms a wide circle or loop in the submucosa (Plate V(*b*)) and it is a common arrangement for the venous channel to join the arterial branch at an acute or right angle At the point of junction the lumen of the vessel narrows and it is clear from preliminary histological work not yet completed that at this point

some anastomoses show a considerable thickening of the muscle coat of the vessel wall

Much still remains to be discovered about these short circuiting channels in regard to their distribution minute *anatomy and control but it seems safe to* assume that they are concerned *in the rapid distribution of blood in* the stomach wall during different phases of gastric activity

SUMMARY

The mucous membrane of the stomach has a rich blood supply consisting of arborizing leashes of capillaries which appear to fill almost completely the glandular layer like a vascular sponge The arrangement of vessels in the mucosa is the same in all parts of the stomach

The capillaries of the mucosa are supplied by long mucosal arteries about 120 microns in diameter (in the fixed specimen) which cross the submucosa obliquely to penetrate the muscularis mucosae and reach the glandular layer In the anterior and posterior walls of the stomach these mucosal arteries arise from an extensive plexus of large vessels in the submucosa which in turn is supplied *by branches from the arterial chains on the greater and lesser curves In the pyloric* region there is a similar arrangement except that the plexus in the submucosa consists of smaller vessels

In the region of the lesser curve the mucosal arteries *do not arise from a plexus* of vessels within the stomach wall but have their origin outside the stomach directly from the left gastric chain The slender vessels pierce the stomach wall to enter the submucosa which they traverse in an oblique manner without the formation of a submucous plexus to reach the mucosa and supply it in a manner similar to that seen in the rest of the stomach wall The vascular arrangement in the lesser curve region gradually merges with that in the anterior and posterior walls

There is wide connection of the mucosal arteries throughout the stomach by *their free anastomosis as they approach the muscularis mucosae* and again on the glandular aspect of that muscle The freely anastomotic nature of the vessels of the stomach wall is perhaps its most notable feature There are no anatomical end arteries The mucosa lies within a large vascular *network consisting of* anastomosing mucosal arteries and the submucous plexus of large vessels in communication with the arterial chains on the greater and lesser curves Whatever the physiological mechanism of control may be channels exist capable of bringing large quantities of blood to the mucosa or of transferring blood from one point to another in the stomach wall

The shift of blood in the stomach wall is further facilitated by a mechanism for short circuiting the mucosal arteries directly into the veins These direct arterio venous channels up to 140 microns in diameter commonly arise from the mucosal arteries and their presence suggests a rapid means of directing blood into or away from the mucous membrane by purely local action and with the minimum *of vascular effort* The general arrangement of the vascular pattern in the stomach wall is summarized in Plate VI It opens up intriguing possibilities of inquiry in both normal and diseased states of the human stomach

REFERENCE

Walder D N (1950) *Lancet* 1 162

CHAPTER 14

GASTRITIS

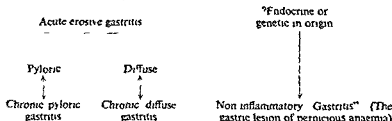
H A MAGNUS

IT is customary to use the term gastritis to cover all the non neoplastic lesions of the gastric mucosa in which direct invasion by pathogenic organisms can be eliminated It is in this sense that the term will be used Towards the end of the nineteenth century pathologists described extensive changes in the gastric mucosa but these were later shown to be due to post mortem autolysis and were discredited In more recent times however the morbid anatomical changes produced in the gastric mucosa by various agents have been studied in partial gastrectomy specimens or in material fixed soon after death

The pathology of gastritis here described is based on the writer s own observations made on some 50 stomachs fixed soon after death and on 635 partial gastrectomy specimens The techniques used for the investigations and many of the results obtained have been fully described elsewhere (Magnus 1937 Magnus and Rodgers 1938 Magnus and Ungley 1938 Magnus 1946)

CLASSIFICATION OF GASTRITIS

Two types of gastritis can be recognized—an inflammatory type and a non inflammatory type which in the writer s experience is only found in association with pernicious anaemia The inflammatory lesion may be seen in either an acute or a chronic phase and it may be localized to the pyloric antrum or be diffuse It is possible therefore to classify gastritis as follows



THE MORBID ANATOMY OF GASTRITIS

This will be considered under three headings

Acute erosive gastritis
Chronic gastritis
The gastric lesion of pernicious anaemia

Acute erosive gastritis

This lesion may be diffuse or localized to the pyloric antrum Acute diffuse erosive gastritis is more frequently endogenous in origin and may be found in patients dying from acute specific fevers Nyfeldt and Vimtrup (1932) have described it in children dying from diphtheria and it has been produced experimentally in animals *with* diphtheria toxin by Hayem (1905) and Thomsen (1925) Acute erosive gastritis localized to the pyloric antrum is generally regarded as exogenous in origin and is found as a rule associated with chronic ulceration of the stomach but it may also occur as a *definite entity in itself with* no evidence of chronic gastric ulceration It is important to realize that gastritis is a condition which occurs in waves each acute exacerbation doing a little more damage to the mucosa so that changes to be described under chronic gastritis may be present in association with the acute condition Whether the lesion be diffuse or localized to the pyloric antrum the morbid anatomy remains the same

Macroscopic appearances

The gastric mucosa is red and oedematous and is covered by a patchy layer of adherent mucus Multiple erosions varying in size from a pin s head to several millimetres in diameter and in number from a few to over a hundred are present Their floors are covered by greyish white fibrinous material These erosions have an elongated ovoid shape and are usually situated on the summits of rugae The *mucosa surrounding them is raised and oedematous giving them a funnel shaped* appearance

Externally the peritoneal coat may be congested and the stomach wall may feel firm and somewhat rigid but these external evidences of inflammation are uncommon

Microscopic appearances

The interstitial tissue of the mucosa is intensely infiltrated by large numbers of polymorphonuclear leucocytes together with lymphocytes plasma cells and eosinophils in smaller numbers (Figs 129 and 130) The polymorphonuclear *leucocytes are present in largest numbers in the subepithelial layer and in the gastric* tips which in many cases are distended by sero fibrinous exudate (Fig 131) This exudate is frequently present in this situation in acute gastritis and stains bright red with eosin It is usually most intense around dilated and congested capillaries Haemorrhages into the interstitial tissue are not found as a rule either at the site of or remote from erosions Occasionally however recent massive interstitial haemorrhages are present but these occur in partial gastrectomy specimens and are produced at the time of the operation *when clamps are applied The mucosal* capillaries are very dilated and congested and contain many leucocytes but thrombosis is absent

The glands may be widely separated by the intense interstitial cellular infiltration The gland cells are in various stages of necrosis and advanced degeneration In some cases desquamated epithelium together with many polymorphonuclear leucocytes fill the gland luminae—glandular erosion (Fig 132) When body mucosa is involved the glands are not so *widely separated from each other The most marked* change is in the chief cells These are shrunken their nuclei pyknotic and quite



Fig 129 —Acute exacerbation of chronic gastritis There is intense cellular infiltration of the stroma Note the sparsity of gland parenchyma due to previous acute exacerbations H and E × 60

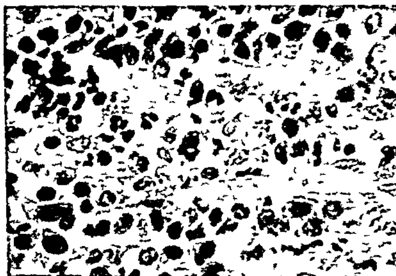


Fig 130 —Higher power of Fig 129 showing an area in which polymorphonuclear leucocytes are plentiful H and E × 900



FIG 131 —Sero fibrinous exudate in the gastric tips H and E × 124

FIG 132 —Glandular erosion H and E × 138

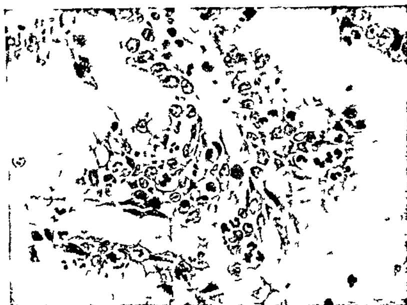


FIG 133 —Vacuoles containing polymorphonuclear leucocytes lying between the cells of the surface epithelium H and E × 500



FIG 134 —Higher power of Fig 133 H and E × 900



FIG 135 —Normal surface epithelium H and E × 445

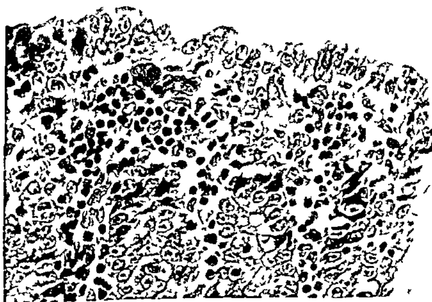


FIG 136 —The surface epithelium in acute gastritis H and E × 445

frequently fragmented The parietal cells are much more resistant and as a rule show little change Sometimes all that remains of a group of glands are several small collections of parietal cells Glandular erosions also occur in the glands of the body mucosa

The surface epithelium shows striking changes Perhaps the most remarkable is the presence between the cells of vacuoles which contain polymorphonuclear leucocytes (Figs 133 and 134) It will be remembered that polymorphonuclear leucocytes are most abundant in the subepithelial layer of the interstitial tissue and they are also present in large numbers in the overlying mucus These facts suggest therefore that there is a transmigration of polymorphonuclear leucocytes through the surface epithelium *via* these vacuoles which are present in large numbers This phenomenon has not been seen apart from its association with acute erosive gastritis and next to the presence of erosions may be taken as a sure sign that an acute exacerbation of the inflammatory process has occurred

The cells of the surface epithelium also show marked changes They are no longer tall and columnar with an almost clear cytoplasm (Fig 135) but are flattened and cuboidal with a darkly staining cytoplasm and show frequent mitotic figures (Fig 136) Often the cells are reduplicated to form a layer several cells thick The limiting membranes of the cells become blurred and the appearance resembles that of a syncytium

The typical erosion involves only the superficial part of the mucosa (Fig 137) If it extends through the mucosa and muscularis mucosae into the submucosa it acquires more serious clinical potentialities and should then be regarded as an acute peptic ulcer The floor of the erosion is composed of fibrinoid material covered by a small amount of exudate containing polymorphonuclear leucocytes Deep to the floor the interstitial tissue is oedematous and infiltrated by polymorphonuclear leucocytes and round cells No evidence of fibrosis is seen around the erosion which presumably heals without leaving a scar All the erosions seen in the material examined had a floor composed of fibrinoid material and none was so small that it could not have been seen with a hand lens The submucosa is somewhat oedematous and may contain polymorphonuclear leucocytes and the vessels here and also in the muscle coat and serosa are dilated and congested

Chronic gastritis

In common with acute gastritis the chronic form shows a marked predilection for the pyloric antrum although it occasionally involves the whole mucosa of the stomach Its hall mark is atrophy of the glandular parenchyma of the gastric mucosa It represents the end result of repeated injuries inflicted by many attacks of acute inflammation

Macroscopic appearances

The gastric mucosa in chronic gastritis apart from evidence of an acute exacerbation very commonly shows no naked-eye abnormality even though histologically a severe degree of gastritis is present

In collaboration with Rodgers (Magnus and Rodgers 1938) the writer examined partial gastrectomy specimens obtained from patients previously gastroscoped and in many cases the appearances of the mucosa and the conclusions reached by



Fig 137.—A typical erosion H and E × 110

Fig 138.—*Etat mammelonné* H and E × 33

gastroscopy bore little or no relation to what was found on histological examination It is easy to overlook the fact that the gastric mucosa is an extremely mobile structure contracting and expanding on a loose elastic submucosa

However in some cases of chronic pyloric gastritis the mucosa of the pyloric antrum may be very flat and have a glistening appearance the areae gastricae being almost invisible In others the muscle coat in the pyloric antrum may be thicker than normal and give a somewhat firm rigid feeling to this region The serosal coat as a rule is normal but it may sometimes be congested especially if there be an acute exacerbation of the inflammatory process in the mucosa

The writer has yet to see an example of hyperplastic gastritis a condition which is stressed so much by many continental writers An appearance which is seen in the normal stomach and may be mistaken for hyperplasia is the occurrence of a condition referred to in the literature as *etat mammelonne* and which is to be regarded as an exaggeration of the normal and not as a pathological state (Fig 138) In *etat mammelonne* the gastric areas are unduly prominent due to an increase in depth of the furrows surrounding them This appearance may be seen in normal stomachs or be associated with the changes of chronic gastritis It may involve normal body mucosa in a stomach showing chronic pyloric gastritis or it may be confined to the pyloric antrum and be associated with the chronic gastritis Measurements of the depth of the mucosa in sections of these abnormal areae gastricae show that it is no greater than the average depth of normal mucosa It is only the abnormal depths of the furrows which make it so appear It should be regarded as an exaggeration of normal structure comparable to lingua plicata and not as a pathological lesion

Microscopic appearances

The most striking change is a very considerable diminution in the number of glands present and a corresponding increase in the amount of interstitial tissue (Fig 139) Of the surviving glands some may show little change whilst in others the lining cells are in various stages of degeneration Frequently adenoma like structures are produced by groups of surviving glands being cut off and surrounded by proliferating connective tissue Occasionally some of the glands dilate to form cysts which are lined by flattened cubical cells—so-called chronic cystic gastritis (Fig 140)

If body mucosa is involved the changes in the glands are even more striking (Fig 141) In many glands the chief cells show advanced degeneration or have disappeared but the parietal cells frequently survive Sometimes whole glands have disappeared leaving small isolated groups of parietal cells in the interstitial tissue In other cases the neck chief cells proliferate and grow down into the glands replacing the destroyed chief cells so that glands are produced which closely resemble pyloric glands (pseudo pyloric glands) (Figs 142 and 143)

The interstitial tissue is considerably increased and the mucosa therefore does not become as thin as it would otherwise do In normal mucosa the interstitial tissue is sparse and consists for the most part of reticulum fibrils but in chronic gastritis the increase of interstitial tissue is due to the replacement of argyrophil fibre by newly formed collagen The interstitial tissue is intensely and diffusely infiltrated with plasma cells Lymphocytes eosinophils and Russell s body cells

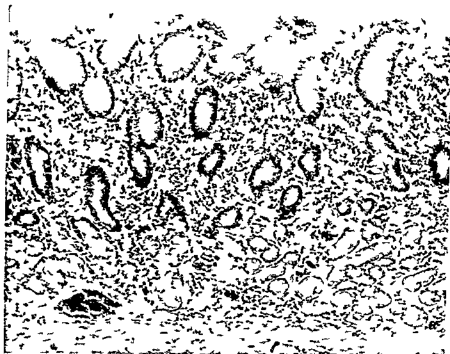


FIG 139—Atrophic gastritis involving pyloric mucosa H and E × 102

FIG 140—Chronic cystic gastritis H and E × 102

Fig 141 —Atrophic gastritis involving body mucosa H and E × 102



Fig 142 —An area of pseudo-pyloric glands around a central area of normal pyloric glands H and E × 102



Fig 143 —Pseudo pyloric glands on the right hand side normal body glands on the left H and E × 400

Fig 144 —Chronic follicular gastritis H and E × 55

are present in smaller numbers The plasma cells are usually in greater numbers in the outer half of the mucosa whilst the lymphocytes are most abundant in the inner half near the muscularis mucosae Here they may be arranged diffusely or be collected to form lymph follicles with germinal centres resting on the muscularis mucosae Sometimes the lymph follicles are very numerous and extend throughout the mucosa in all directions They then frequently make their way through the muscularis mucosae into the submucosa When the lymph follicles are as well developed as this the condition is sometimes called chronic follicular gastritis (Fig 144)

The cells of the surface epithelium and pits may be normal or they may show that state of activity so typical of an acute exacerbation already described Intestinal epithelium is frequently found in mucosa showing the changes of chronic gastritis (Fig 145) It is identical with true intestinal epithelium (Magnus 1937) It has not been found in normal mucosa and its presence there as an example of congenital heterotopia must be very rare Its occurrence in association with chronic gastritis is to be regarded as an example of metaplasia of the surface epithelium the result of chronic irritation from repeated attacks of gastritis When the chronic gastritis is localized to the pyloric antrum intestinal epithelium has not been seen in the normal body mucosa but when the gastritis is diffuse it is found as frequently in the body as in the pyloric mucosa

In chronic pyloric gastritis the muscularis mucosae in the pyloric region is thickened and there is an increase in fibrous tissue in all the coats of the stomach wall but especially in the submucosa which may also contain lymph follicles Quite frequently also the submucosa and muscle coat are diffusely infiltrated with plasma cells and lymphocytes

The gastric lesion of pernicious anaemia

In 1938 together with Ungley the writer described a characteristic lesion occurring in the body mucosal region of the stomach in patients dying with pernicious anaemia The original observations were made on 7 cases but since then 10 further cases have been examined and the same lesion has been found in every case It has not yet been seen in association with any other disease process Many of our findings have been confirmed by other workers notably Cox (1943)

In all the material examined the stomach and a varying length of intestine has been fixed soon after death In the last 10 cases examined an effort was made to fix as much of the gastro intestinal tract as possible by forcing fixative down the stomach tube with a Higginson s syringe In 6 cases fixation was excellent down to the lower end of the jejunum and in 2 of these the whole of the jejunum and the first part of the ileum was also well fixed

Macroscopic appearance of stomach

The naked eye changes observed have been identical in all cases The upper two thirds of the stomach—that is the region of the body mucosa—has shown a severe atrophy so that this area is reduced to the thinness of parchment At the junction of the body with the pyloric mucosa however there is a transition usually abrupt to the normal thickness of the stomach wall and this is maintained throughout the whole of the pyloric antrum and duodenum The mucosal surface

FIG 145 —An area of intestinal epithelium in pyloric mucosa stained with haematoxylin and mucicarmine to demonstrate the goblet cells × 130



FIG 146 —The normal thickness of the stomach wall in the body mucosa area H and E × 9



FIG 147—The thickness of the stomach wall in the body mucosa area in pernicious anaemia H and E × 9

FIG 148—Normal body mucosa H and E × 10?

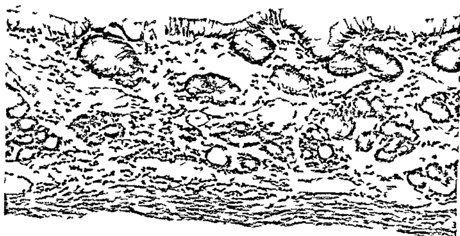


FIG 149—Body mucosa of the stomach in pernicious anaemia H and E × 138

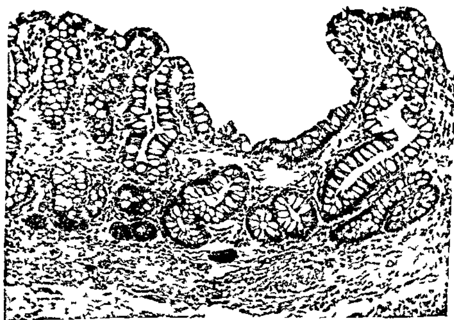


FIG 150—Intestinal epithelium in the body mucosa area from a pernicious anaemia stomach H and E × 115

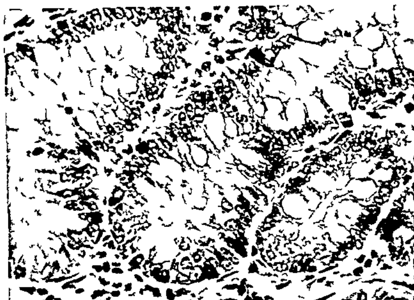


FIG 151 —Argentaffine cells in the stomach of an untreated case of pernicious anaemia Masson s silver impregnation × 430

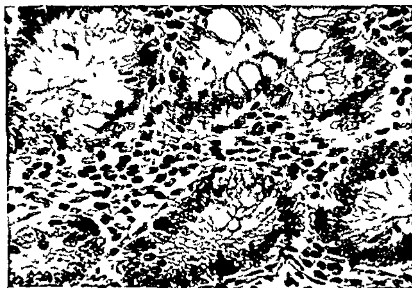


FIG 152 —Argentaffine cells in the stomach of a case of pernicious anaemia fully treated for 9 years and dying from a cerebral haemorrhage Masson s silver impregnation × 430

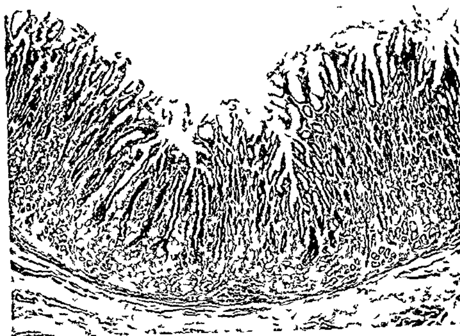


FIG 153 —Normal pyloric mucosa H and E × 33

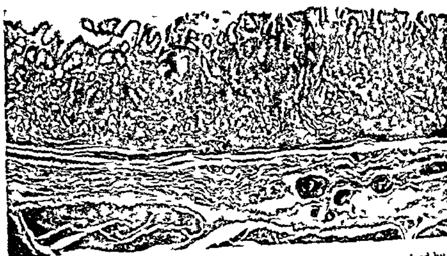


FIG 154 —Pyloric mucosa from a pernicious anaemia stomach It is not involved by the atrophic process H and E × 33

in the upper atrophic region is flattened and areae gastricae can no longer be seen whilst in the pyloric region the mucosal surface is normal

These macroscopic appearances are so striking and characteristic that it is possible to recognize the stomach from a case of pernicious anaemia by naked eye examination alone

Microscopic appearances of stomach

Histological examination confirms the naked eye distribution of the atrophy In the body mucosal region there is a severe atrophy involving all the coats of the stomach wall (Figs 146 and 147) and it is clear that the parchment like thinness observed macroscopically is not due to mucosal atrophy alone

In the mucosa (Figs 148 and 149) all that remains is the surface epithelium and a few scattered glands lined by mucus producing cells whilst the specialized oxyntic and peptic cells have entirely disappeared Yet in spite of this there is a complete absence of fibrosis cellular infiltration obliterative endarteritis or other evidence of past inflammation and there is a corresponding absence of fibrosis in the sub mucosa and subserosa The muscle coat shows atrophy but here also there is an absence of fibrosis

In 12 of the stomachs examined large areas of intestinal epith lium were present in the atrophic body mucosa (Fig 150) and sometimes al o patchily in the pyloric mucosa if this was the seat of ordinary atrophic pyloric gastritis It has been shown elsewhere (Magnus 1937) that intestinal epithelium occurring in the stomach has all the characteristics of true intestinal epithelium It is not surprising there fore that many argentaffine cells were present in the glands of Lieberkuhn (Figs 151 and 152) The significance of this finding will be discussed in a later section

In some of the stomachs there was a variable degree of inflammatory atrophic gastritis involving the pyloric mucosa but this had no special features and there was no atrophy involving all layers (Figs 153 and 154)

Microscopic appearances of small intestine

In those cases in which much of the small intestine was well fixed special attention was paid to the frequency of occurrence and distribution of argentaffine cells

In man the argentaffine cell may be found in gastro intestinal mucosa anywhere from the cardia of the stomach to the lower end of the rectum but it is most abundant lying between the cells lining the glands of Lieberkuhn in the duodenum As the intestine is followed down the argentaffine cell becomes less frequent so that by the time the large bowel is reached several sections may have to be searched before one cell is found Apart from its constant occurrence in the stomach in association with heterotopic intestinal epithelium the argentaffine cell is only observed occasionally in the gastric and pyloric glands

In the 6 of the last 10 cases examined in which much of the small intestine was well fixed the frequency of occurrence of the argentaffine cell in the duodenum jejunum and ileum was compared with controls obtained by removing strips of mucosa during various enterostomy operations in patients not suffering from pernicious anaemia In every case argentaffine cells were abundant throughout and showed no difference in their frequency of occurrence as compared with the controls (Figs 155 156 and 157) This finding will be discussed in a later section

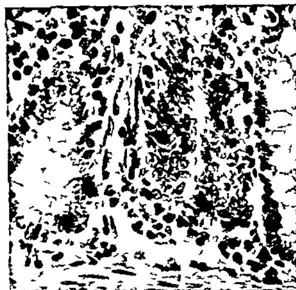


(a)



(b)

FIG 155 —(a) Argentaffine cells in the duodenum from a case of pernicious anaemia (b) argentaffine cells in a control duodenum Masson's silver impregnation × 430



(a)



(b)

FIG 156 —(a) Argentaffine cells in the jejunum from a case of pernicious anaemia (b) argentaffine cells in a control jejunum Mas on s silver im pregnation × 430



(a)



(b)

FIG 157 —(a) Argentaffine cells in the ileum from a case of pernicious anaemia (b) argentaffine cells in a control ileum Masson's silver impregnation × 430

FREQUENCY OF OCCURRENCE OF INFLAMMATORY GASTRITIS

Inflammatory gastritis may be produced by many exogenous and endogenous factors It is unlikely therefore that many people during their lifetime will escape at least one attack of acute gastritis with its accompanying damage to the gland parenchyma and surface epithelium It is extremely unlikely that such specialized cells as those lining the glands of the gastric mucosa can be replaced when once destroyed so that each attack of inflammation will produce more damage to glands more atrophy and more cellular infiltration of the mucosa and submucosa—the picture of chronic gastritis The vast majority of stomachs examined therefore will and do show the changes of chronic gastritis either pyloric or diffuse Need such a condition however be accepted as necessarily an active pathological lesion for in many cases it appears to be quiescent?

It would seem more reasonable to assume that the vast majority of people during their lives have attacks of acute gastritis which however rapidly heal and produce the picture of quiescent chronic gastritis which is symptomless and harmless In a certain proportion of individuals for reasons unknown the acute inflammation does not subside when the cause is removed but it persists or frequently recurs resulting eventually in the formation of a chronic gastric ulcer

If this view be accepted it will assist in explaining the great frequency with which chronic quiescent gastritis is found in post mortem material not associated with chronic ulceration or any other lesion and not accompanied by any symptoms in life It may perhaps be compared to the great frequency with which quiescent healed apical tuberculous lesions are found in post mortem examination of the lungs which were not accompanied in life by any symptoms because the lesions were quiescent and healed

Nevertheless it is well known that as age advances anacidity becomes more common Davies and James (1930–31) found a histamine refractory achlorhydria in 15 out of 100 patients examined over the age of 60 Bloomfield and Polland (1933) found histamine refractory achlorhydria in over 30 per cent of cases over the age of 60 More recently Wood and his colleagues (1949) have carried out gastric biopsies in 54 patients studied to determine the relation between gastric secretion and the histological appearance of the mucosa of the body of the stomach They found a clear cut relationship between the severity of the atrophic gastritis seen in the biopsy specimen and the degree of achlorhydria present These workers have therefore provided histological support for the suggestion made by the writer in 1937 that the progressive increase in the number of cases of anacidity in each decade is probably the result of an organic lesion of the gastric mucosa.

GASTRITIS AND PEPTIC ULCERATION

It is important to realize that body mucosa in small or large amount, was [illegible] in practically all the 600 partial gastrectomy specimens examined so [illegible] possible to determine whether the gastritis was diffuse or localized [illegible] antrum that is the pyloric mucosa and perhaps the first [illegible] body mucosa If the remainder of the body mucosa in the [illegible] is reasonable to assume that the body mucosa left behind in the [illegible] also and vice versa

Of the 284 specimens containing active gastric ulcers or the scars of healed ulcers only 20 (7 per cent) showed macroscopic erosions in the pyloric antrum —acute erosive pyloric gastritis This figure is not in agreement with Puhl s (1926) figure of 27 1 per cent or Konjetzny s (1930) figure of 100 per cent The latter figure includes many cases in which only microscopic erosions were present

Whilst the macroscopic picture of acute gastritis was rare in the material examined histologically it was not uncommon to see in the pyloric mucosa trans migration of polymorphonuclear leucocytes through the surface epithelium associated with great activity of the cells of the latter suggesting that an acute exacerbation of gastritis was present or had recently occurred

In all the specimens examined chronic gastritis was present having the same pathological features as those already described

In 70 cases (26 5 per cent) it was diffuse involving body as well as pyloric mucosa and in the remainder it was localized to the pyloric antrum (73 5 per cent)

TABLE I

FREQUENCY AND DISTRIBUTION OF INFLAMMATORY GASTRITIS IN 540 PARTIAL GASTRECTOMY SPECIMENS REMOVED FOR PEPTIC ULCERATION

	Acute erosive gastritis	Chronic atrophic gastritis
Gastric ulceration – – – 284 specimens	20 (7%)	264 (93%) Diffuse 70 (26 5%) / Pyloric antrum 194 (73 5%)
Duodenal ulceration – – *256 specimens*	Very occasional and of *mild degree*	Localized to pyloric antrum in all *cases—256 (100%)*

It will be seen from these figures (summarized in Table I) that gastritis was present in every case It was usually severe in degree with much destruction of gland parenchyma fibrosis and cellular infiltration Intestinal epithelium was present in many cases and in a few it had replaced the entire gastric mucosa examined only a few areas of degenerate gastric glands remaining

It is frequently stressed in the literature that a distinction can be made between ulcer gastritis and cancer gastritis It may be stated here that the writer has never been able to demonstrate any differences in the gastric mucosa in these two disease processes The degree of atrophy was just as severe in the ulcer cases as in the cancer cases and intestinal epithelium said to be much more frequent in cancer gastritis was actually less frequent

In the 256 partial gastrectomy specimens removed for duodenal ulcer a mild quiescent chronic gastritis was present localized to the pyloric antrum with moderate atrophy of the gland parenchyma Intestinal epithelium was present in only a few cases and erosions or other signs of activity were seldom seen In those cases in which a portion of the duodenum was included in the specimens the inflammatory changes present in the duodenal mucosa were also of a mild nature with little or no destruction of the glandular parenchyma

Puhl (1926) found erosive gastritis as frequently in association with duodenal ulcer as with gastric ulcer and similar findings are recorded by other German workers In America however Walters and Sebening (1932) and other workers state that erosive gastritis is very seldom found in association with duodenal ulcer and that the pyloric gastritis present is of a mild character

The gastritis present in association with peptic ulceration shows no specific characteristics and resembles in every way the acute and chronic inflammatory gastritis seen apart from chronic ulceration

GASTRITIS AND GASTRIC CANCER

Konjetzny and Hurst have for long presented eloquent arguments to show that cancer of the stomach develops on the basis of a chronic gastritis In his Schorstein lecture in 1929 Hurst stated that a diffuse atrophic gastritis accompanied by achlorhydria preceded the development of cancer of the stomach in 75 per cent of cases and that it should in fact be regarded as a pre cancerous state Konjetzny in numerous papers strongly supported this view and in addition stressed the severity of the atrophy present in association with carcinoma and described numerous changes which he regarded as pre-cancerous and in which he could observe transition stages to malignant growth These hyperplastic changes so called atrophic hyperplastic gastritis consist of wart like polypoidal outgrowths of the surface epithelium accompanied in some cases by tubular downgrowths of the epithelium in such areas into the mucosa and underlying submucosa

Of the 95 partial gastrectomy specimens removed for carcinoma 83 contained primary growths and 12 contained typical ulcer cancers

In the 83 specimens containing primary carcinomas the gastritis was diffuse in 11 (13 2 per cent) and isolated to the pyloric antrum in 72 cases (86 8 per cent) in which the body mucosa was perfectly normal *In the 12 specimens containing* ulcer cancers the gastritis was localized to the pyloric antrum in all cases (*see* Table II)

TABLE II

DISTRIBUTION OF INFLAMMATORY GASTRITIS IN 95 PARTIAL GASTRECTOMY SPECIMENS REMOVED FOR CARCINOMA

	Chronic atrophic gastritis Pyloric antrum	Chronic atrophic gastritis Diffuse
Primary carcinoma - - 83 specimens	72 (86 8)	11 (13 2/)
Ulcer-cancer - - - 12 specimens	12 (100 /)	None

The gastritis present in these specimens was identical in every way with the picture of chronic gastritis which has already been given It differed in no way from the gastritis associated with simple ulcer and was of no greater severity

As in the case of simple ulcer the gastritis when pyloric in distribution involved the entire pyloric antrum and was not localized to the mucosa in the immediate

neighbourhood of the growth In no case were any of the hyperplastic or pre cancerous changes described by Konjetzny observed

In the 72 cases of primary carcinoma in which the gastritis was localized to the *pyloric antrum the body mucosa* included in the specimens was normal If therefore achlorhydria precedes the formation of gastric cancer as frequently as is stated it is not due to destruction of the parietal cells in the body mucosa

In the 11 partial gastrectomy specimens in which the gastritis was diffuse the atrophy was only mild or moderate in degree and histologically normal parietal cells apparently capable of secreting hydrochloric acid were plentiful

It is in the relationship between gastritis and gastric cancer that an examination of my material has given results which differ greatly from those described in the literature It will be remembered that the majority of observers state that primary *malignant ulceration of the stomach is always associated with a severe diffuse* atrophic gastritis which is to be regarded as a pre cancerous state and in which pre cancerous hyperplastic lesions can be recognized In my material the gastritis *was similar in every respect to that found in association with peptic ulceration* and there were no characteristics by which it could be recognized as cancer gastritis No hyperplastic pre cancerous lesions seen so frequently by Konjetzny and others *were present in any of the specimens*

If the view that a healed quiescent inflammatory gastritis is present in the vast majority of stomachs be correct it would be surprising if such a gastritis were not found in association with carcinoma Such indeed has been the case for in nearly all the partial gastrectomy specimens the gastritis present in association with the carcinoma has been a quiescent atrophic gastritis indistinguishable from that seen in otherwise normal post mortem stomachs and in association with peptic ulceration

Whilst of course the relationship between chronic irritation and neoplasia cannot be denied it seems unlikely that this quiescent lesion is the essential basis on which cancer develops It is stated that post inflammatory hyperplasia leading to papillomatous overgrowth is the specific pre cancerous lesion If this were so some degree of papillomatous hyperplasia should have been present in the material examined but in no case was this discovered

THE GASTRIC LESION OF PERNICIOUS ANAEMIA

Fenwick (1880) was the first in Great Britain to describe atrophy of the gastric mucosa in pernicious anaemia He recorded 4 cases of essential anaemia in all of *which there* was atrophy of the stomach and especially of the gastric mucosa Nothnagel (1879) almost at the same time described similar findings but in all these cases the stomachs were unfixed and the histology uncertain In 1900 however Faber and Bloch published the first of their papers in which they described their findings in material fixed soon after death They examined the stomachs from 8 patients dying from pernicious anaemia and found a diffuse gastritis in every case

Wallgren (1923–25) examined the gastro intestinal tracts of 16 cases of pernicious anaemia and 2 cases of aplastic anaemia He found a diffuse atrophy of the gastric mucosa in all the cases of pernicious anaemia but the stomach was normal in the two cases of aplastic anaemia More recently *Brown (1934) has analysed the autopsy*

records of 42 cases of pernicious anaemia He states that the picture of chronic gastritis was present in all but one case and stresses the absence of acidophil cells in all but 5 cases but his material was presumably unfixed Jones Benedict and Hampton (1935) record the gastroscopic surgical and radiological examination of 5 typical cases of pernicious anaemia which were observed over a long period They present evidence which they believe indicates that atrophy of the stomach occurs particularly during a relapse and not as an invariable accompaniment of the disease They observed hypertrophic gastritis during a relapse and also during the early stages of a remission but after specific treatment of the anaemia atrophy and hypertrophy of the gastric mucosa both tended to disappear

Up to 1938 therefore practically all the stomachs examined had been unfixed and the emphasis in the histological findings had been on a diffuse inflammatory lesion The investigations of the writer and Ungley however have been carried out from that time to the present on gastro intestinal tracts fixed very shortly after death Cox (1943) in America has also investigated the gastro intestinal tract in pernicious anaemia in a similar manner

These investigations show that the gastric lesion consists of a profound atrophy involving all coats of the stomach wall and localized in its distribution to the body mucosa region Many still believe that this atrophic lesion is the end result of an inflammatory gastritis but this is most unlikely None of the criteria of a chronic inflammatory process is present and a lesion similar to the gastric lesion has not yet been seen in association with any other disease In pernicious anaemia the pyloric mucosa is usually normal but may show mild changes of inflammatory atrophic gastritis This is a reversal of the usual finding in which the inflammatory lesion usually hits the pyloric antrum leaving the body mucosa untouched a diffuse inflammatory gastritis only being found in 26 5 per cent of cases in association with simple ulceration and in 13 2 per cent in association with malignant ulceration

It appears to be far more likely that the gastric lesion is congenital in origin and fundamental in the understanding of the aetiology of pernicious anaemia Against this conception it has been stated by some gastroscopists that following treatment the body mucosa of the stomach returns to normal others believe that an atrophy of the body area of the stomach is not an invariable finding in pernicious anaemia (Jones Benedict and Hampton 1935 Schindler and Serby 1939 Hardt Schwartz and Steigmann 1948)

Amongst the writer s 17 cases 4 had been adequately treated for pernicious anaemia for from 5 to 13 years before death These 4 cases all showed the gastric lesion with no evidence of regeneration of the body mucosa and the reappearance of the specialized cells Doig and Motteram (1950) mention one case of p rnicious anaemia on whom they carried out gastric biopsy after 2 years treatment from the time of diagnosis his haemoglobin being 15 7 grams per cent at the time of biopsy They found the typical gastric lesion in their material

There would appear to be support therefore for the belief that the gastric lesion is a fundamental morbid anatomical lesion in pernicious anaemia and that it is highly likely that it persists unaltered however long the patient may be treated

In 1939 Jacobson as a result of the investigation of the gastro intestinal tracts in 12 cases of pernicious anaemia and 2 cases of sprue with macrocytic anaemia

stated that in all these cases there was either complete or almost complete absence of argentaffine cells in the mucosa of the gastro intestinal tract

In the original paper on the gastric lesion in pernicious anaemia (Magnus and Ungley 1938) it was pointed out that in several of the seven cases in that series large areas of intestinal epithelium were present in the atrophic body mucosa This intestinal epithelium, as one would expect contained many argentaffine cells The writer (1940) expressed the opinion that there appeared to be a serious discrepancy between these findings and those of Jacobson In a later paper Jacobson and Williams (1945) state that the finding of argentaffine cells in metaplastic islands of intestinal epithelium in the stomach does not exclude the possibility of argentaffine cells playing an important part in normal erythropoiesia since in pernicious anaemia the areas of gastric mucosa which show intestinal metaplasia with argentaffine cells are small compared to the whole area of the gastric mucosa

In 12 of the 17 stomachs examined large areas of intestinal epithelium were present in the atrophic body mucosa area and sometimes some were also present in the pyloric mucosa if this was the seat of ordinary atrophic pyloric gastritis Wherever there was intestinal epithelium argentaffine cells were numerous

In six cases the small intestine down to the lower jejunum and in two of these cases as far down as the ileum was well fixed allowing a comparison to be made between the number of argentaffine cells present in the duodenum jejunum and ileum with controls

In every case argentaffine cells were abundant in the duodenum and comparison with the control duodenal specimens showed no difference in their numbers distribution or appearance The same was true of the jejunum although here the cells got less numerous as one travelled downwards as was to be expected In the two specimens in which the ileum was fixed argentaffine cells were still numerous and occurred as frequently as in the lower part of the jejunum

From an examination of the writer s material therefore it must be concluded that there is no evidence of a reduction in the number of argentaffine cells found in the gastro intestinal tract in pernicious anaemia Indeed in some cases in which intestinal metaplasia in the body was very marked it would appear that there is an increase rather than the reverse

REFERENCES

Bloomfield A L and Polland W S (1933) *Gastric anacidity its relation to disease* New York Macmillan
Brown M R (1934) *New Engl J Med* 210 473
Cox A J (1943) *Amer J Path* 19 491
Davies D T and James T G I (1930-31) *Quart J Med* 24 1
Doig R K and Motteram R (1950) *Aust N Z J Surg* 19 296
Faber K and Bloch C F (1900) *Z klin Med* 40 98
Fenwick S (1880) *On atrophy of the stomach and on the nervous affections of the digestive organs* London Churchill
Hardt L L Schwartz S O and Steigmann F (1948) *Gastroenterology* 10 108
Hayem G (1905) *Bull Soc Med Hôp Paris* 20 145
Hurst A F (1929) *Lancet* 2 1023
Jacobson W (1939) *J Path Bact* 49 1
— and Williams S M (1945) *Ibid* 57 423
Jones C M Benedict E B and Hampton A O (1935) *Amer J med Sci* 190 596

REFERENCES

Konjetzny G E (1930) *Die ent undliche Grundlage d r typischen Geschwursbildung im Magen und Duodenum* Berlin Springer

Magnus H A (1937) *J Path Bact* 44 389

— (1940) *Brit med J* 1 415

— (1946) *J Path Bact* 58 431

— and Rodgers H W (1938) *St Bart s Hosp Rep* 71 129

— and Ungley C C (1938) *Lancet* 1 4 0

Nothnagel H (1879) *Dtsch Arch klin Med* 24 353

Nyfeldt A and Vimtrup B (1937) *Acta med scand* 78 447

Puhl H (1926) *Virchows Arch* 265 160

Schindler R and Serby A M (1939) *Arch intern Med* 63 334

Thomsen E (1935) *Acta med scand* 61 377 57.

Wallgren T (1923-25) *Arb path Inst Univ Helsingf N F* 3 275

Walters W and Sebening W (1932) *Minn Med* 15 579

Wood I J Doig R K Motteram R Weid n S and Moore A (1949) *Gastro nterology* 12 949

CHAPTER 15

GASTRIC BIOPSY USING A FLEXIBLE GASTRIC BIOPSY TUBE

R K DOIG AND I J WOOD

THE purpose of this chapter is to describe a flexible gastric biopsy tube which was designed in the Clinical Research Unit of the Walter and Eliza Hall Institute of *Medical Research and the Royal Melbourne Hospital*

The understanding of disease processes in any organ is always increased when material is available for histological examination With regard to the stomach Chevalier Jackson in 1906 was the first to perform gastric biopsy which he did *through his rigid oesophagoscope* (Jackson C and Jackson C L 1935) With the development of the flexible gastroscope by Schindler (1937) and following its widespread use in America Kenamore Scheff and Womack (1946) and Benedict (1948) were led to design operating gastroscopes They used biopsy forceps attached to a flexible gastroscope to obtain fragments of gastric mucosa under vision

Our approach to the technical problem has been from an entirely different direction In 1894 Einhorn observed fragments of mucous membrane in aspirated material from a group of patients with dyspepsia These fragments he recognized as being separated from the mucosa and he called the condition erosive gastritis Hawksley (1939 1948) described the histological appearance in more detail Invariably the section showed acute or chronic gastritis of moderate or severe degree Einhorn was convinced these fragments separated naturally and not by trauma from the tube or from aspiration Hawksley agreed although he suggested that gentle aspiration may separate abnormal tissues along lines of easy cleavage

We also have seen these small fragments in gastric contents Frequently vigorous aspiration could remove a larger fragment and some blood Acting on this observation an instrument was designed to cut off a piece of mucosa rather than tear it away after it had been sucked into the lumen of a tube lying in the stomach Such a technique was primarily used as a research tool but we have come to value it *in the investigation of dyspepsia and rather unexpectedly in the differential* diagnosis of macrocytic anaemia

Instrument and technique

Our flexible gastric biopsy tube (Wood Doig Motteram and Hughes 1949) consists of a length of Bowden wire covered with plastic tubing to render it air tight (Fig 158) At the distal cutting end is a metal cylinder housing a cylindrical knife This knife can be moved up and down past a lateral hole by a wire which passes the whole length of the instrument In preliminary tests it was found that a lateral hole of $\frac{3}{32}$ inch diameter afforded specimens of satisfactory size with no danger of excessive damage to the submucous and muscular layers At the proximal

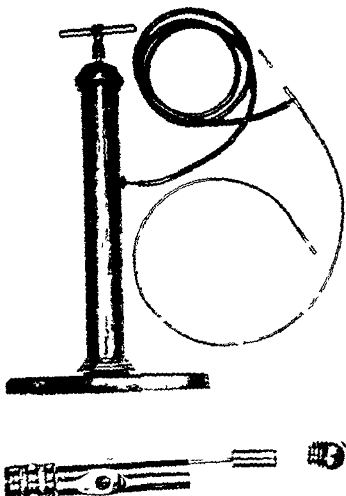


FIG 158 —Flexible gastric biopsy tube Upper photograph shows biopsy tube and exhaust pump connected by rubber tubing. Lower photograph shows cutting end Terminal screw removed Knife pushed down × 1½ (*By courtesy of Gastroenterology and Williams and Wilkins Company*)

This biopsy tube made by Messrs. F I Grimwad nd Dowling Ltd Alfred Place Melbourne Victoria, Australia

operating end a lateral tube is inserted for connection to an exhaust pump so that when suction is applied a fragment of gastric mucosa is pulled through the lateral hole in the far end This fragment is cut off by pulling up the cylindrical knife The metal cylinder is closed by a terminal screw On its removal the cylindrical knife can be forced out to obtain the fragment of mucosa The knife itself can be unscrewed from the wire for cleaning and sharpening All the metal parts are made of stainless steel The overall length of the tube is 100 centimetres and levels I II and III are marked on the tube 45 55 and 65 centimetres from the lateral hole

The biopsy is carried out with the patient fasting for at least 6 hours Surface anaesthesia is produced by the patient gargling in divided lots 15 millilitres of 3 per cent cocaine with adrenaline 1 10 000 A fine rubber stomach tube is then passed into the stomach and this is emptied by tilting the patient and by gentle aspiration with a syringe Complete emptying of the stomach is desirable so that gastric mucosa rather than fluid will be aspirated through the lateral hole of the biopsy tube

With the patient lying on his left side and his head supported by an assistant the biopsy tube is passed Usually it enters the oesophagus and readily passes without discomfort or resistance into the stomach (past level I) Should it be held up at the cardia this can usually be overcome by the patient swallowing or deep breathing or by withdrawing the instrument a little then rotating and re inserting it The instrument passes into the stomach until it engages the body of that organ in the region of the greater curvature and about level II The tube is withdrawn to level 1^{1} before making the biopsy (this is approximately correct for most patients) The side arm is rotated so that the distal lateral hole is away from the lesser curvature In the actual operation the knife is pushed down suction applied and the knife pulled up thus cutting off the fragment of gastric mucosa sucked into the lateral hole The procedure is repeated after a slight alteration in position After withdrawing the biopsy tube the terminal screw is removed and the knife pushed down The fragments may be within the knife more often they are lodged in the metal cylinder or the adjacent portion of the instrument A gentle stream of air down the biopsy tube will blow them out The fragments are immediately put in 10 per cent formol saline If no fragments are obtained the instrument is re introduced and a second attempt made

Immediately after use the instrument is cleaned by sucking water through it and then air till the inside is dry It is sterilized by wiping with Zephiran 1 100 The knife is cleaned in water and then soaked in alcohol It is essential that the knife be sharpened after every 4–5 operations

Gastroscopy may be performed immediately after the biopsy Usually the site of the biopsy can be seen as a small haemorrhagic area After the operation the patient rests for 3 hours When the anaesthesia has worn off a milk drink is given Out patients are seen again in 2 days time

The procedure is tolerated remarkably well There may be an initial discomfort referred to the pharynx The patient can also appreciate pressure on the closed cardia or against the body of the stomach but no sensation accompanies the actual cutting Exceptionally some sedative is necessary to perform the biopsy either because of apprehension or because there has been unrecognized hold up at the cardia at a previous biopsy

Theoretically haemorrhage ulceration and perforation are possible complications In our series of 737 attempted biopsies 7 have shown clinical evidence of bleeding by haematemesis or melaena or sudden collapse and pallor within 48 hours In only two patients was transfusion necessary because of blood loss Two others were admitted to the ward for a short period of observation All made a satisfactory recovery Oesophageal varices or a known haemorrhagic tendency are contra indications to biopsy We have done it with impunity in patients with cirrhosis and hypertension and those patients who have bled have shown no remarkable features except one with unexplained lowered prothrombin level

No patient showed evidence of established ulceration Moreover it is almost impossible to find the lesion in the excised stomach when biopsy is done prior to gastrectomy In the cat Gunter (1950) has shown the lesion in the gastric mucosa heals rapidly The small fragment removed precludes the possibility of perforation

The procedure is not uniformly successful We have obtained satisfactory specimens in 629 of 737 attempts at biopsy In one third of the failures the biopsy has been from the oesophagus Some of the remainder are inadequate but in the majority there has been nothing obtained at all Usually on repeating the biopsy we have been able to obtain a specimen Thus we have had satisfactory sections from 437 of 486 patients Many patients have had numerous biopsies without ill effect

HISTOLOGICAL TECHNIQUE

The fragment of gastric mucosa is fixed in 10 per cent formol saline dehydrated and imbedded in paraffin Care must be taken to ensure its correct positioning in the paraffin block so that the sections will be made perpendicular to the surface The sections are stained with haematoxylin and eosin haematoxylin and mucicarmine and by Motteram s modification of Bowie and Vineberg s stain for pepsinogen granules (Motteram 1951) The fragment of mucosa is usually 2 millimetres in diameter and extends down to the muscularis mucosae (*see* Fig 159)



FIG 159—Biopsy fragment. Normal mucosa This is the ideal specimen with small piece of muscularis mucosae and section cut perpendicular to surface Haematoxylin and Eosin 8

VALUE OF GASTRIC BIOPSY

Our flexible gastric biopsy tube usually obtains specimens from the body of the stomach near the greater curvature as determined by radiological examination and by gastroscopic examination Rarely have we seen the site when the biopsy has been performed 2–3 days prior to subtotal gastrectomy for duodenal ulcer It is therefore of value in studying diffuse lesions in this area The instrument is of no direct value in the study of gastric ulcer and gastric carcinoma as the method is blind A biopsy showing carcinoma has only been obtained on one occasion in our series In gastric ulcer and carcinoma there is usually a zone of inflammation surrounding the lesion so that in these conditions a fragment removed from this zone will show superficial or atrophic gastritis whereas in a more distant area the mucosa may be normal In duodenal ulcer the mucosa from biopsy is usually normal

Our chief interest has been the study of patients who show neither gastroscopic nor radiological evidence of either ulcer or carcinoma but have dyspepsia or an abnormal histamine test meal and patients with pernicious anaemia or subacute combined degeneration of the cord

With few exceptions we have found three main types of lesion in the gastric mucosa which we have classified as superficial gastritis atrophic gastritis and gastric atrophy (Doig and Motteram 1950) Between these categories and normal mucosa no rigid separation is possible each merges into the next although in the typical case no difficulty exists Just as in liver biopsy gastric biopsy is of use only when the lesion is found uniformly throughout the mucosa of the body of the stomach As a check for this diffuseness examination of routine autopsy material is worthless so that we have no direct proof of it However the similarity of appearance when two pieces are obtained and when the biopsy is repeated suggests that gastritis when affecting the body of the stomach is a diffuse lesion We have also shown that with atrophy of the specific glands there is usually achlorhydria and a diminished secretion of pepsin (Wood Doig Motteram Weiden and Moore 1949) Considering test meals on patients with no ulcerative or local lesion in the series normal mucosa to gastric atrophy there is a consistent relation between histological appearance and the total volume of secretion acid and pepsin concentration (Weiden and Funder 1952) and also a steady fall in the amount of fasting contents removed prior to biopsy

The gastric biopsy yields material from the human stomach eminently suitable for analysis of the normal appearance We have not studied this in any great detail but in brief have accepted as normal the following appearances (*see* Fig 160) The epithelium of the gastric ridges and pits is tall columnar in type and regular in appearance The gastric glands are well stained and regular in their arrangements The lamina propria is sparse in amount with very few wandering cells

In superficial gastritis (*see* Fig 161) the histological changes consist of infiltration of the superficial zone with wandering cells including polymorphonuclear leucocytes lymphocytes plasma cells and macrophages The surface epithelium is irregular both in the height of cells and in general arrangement There is little or no atrophy of the chief and parietal cells Rarely have we seen superficial gastritis resolve More often the inflammatory changes remain or there is increasing atrophy of the specific glands so that atrophic gastritis results Once

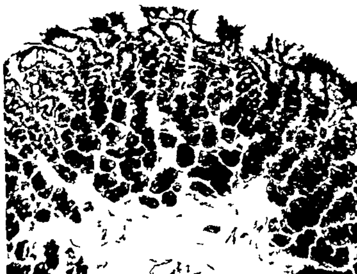


FIG 160—Normal mucosa Regular tall columnar epithelium on surface and in pits Chief cells stained darkly Parietal cells in intermediate zone Minimal wandering cell content Trichrome stain × 175



FIG 161—Superficial gastritis Some heaping of the ridges Only slight decrease in amount of glandular tissue Superficial infiltration with wandering cells Haematoxylin and Eosin × 1 5



FIG 162 —Atrophic gastritis Irregular surface epithelium with downgrowth of pits Atrophy of specific cells with loss of staining qualities Dense cellular infiltration Haematoxylin and Eosin × 130



FIG 163 —Gastric atrophy Intestinal metaplasia of surface epithelium No specific chief or parietal cells Mild cellular infiltration Haematoxylin and mucicarmine 130

this stage has been reached there is little tendency for resolution and regeneration to occur In atrophic gastritis (*see* Fig 162) the inflammatory reaction extends throughout the mucosa and there is partial to almost complete atrophy of the chief and parietal cells We have taken disappearance of more than half the specific cells as the distinction between atrophic and superficial gastritis The surface epithelium is still irregular and may show intestinal metaplasia

Our studies suggest that sup rficial gastritis and more particularly atrophic gastritis may be the direct cause of ill health Symptoms arise more frequently in women over the age of 45 years However the relation between symptoms the personality of the patient and the type and severity of gastritis is far from clear The patients usually complain of chronic epigastric discomfort with flatulence and epigastric tenderness The discomfort may be relieved by alkaline powder but not so completely as in the case of peptic ulcer It is rarely relieved by food The periodicity of symptoms in chronic ga tritis may resemble that seen in peptic ulcer but more often when the disease is active p riods of freedom and periods with symptoms alternate every few days In an exacerbation of symptoms vomiting and even haematemesis may occur (Doig 1949) These exacerbations appear to be brought on by infections malnutrition excessive alcoholic consumption or by severe mental or physical strain

In cases of pernicious anaemia with or without subacute combined degeneration of the spinal cord or when cord degeneration occurs without *haematological* change gastric biopsy usually shows a picture which we have termed gastric atrophy (*see* Fig 163) The greater part of the surface epithelium shows *intestinal* metaplasia Specific cells are rarely found and the cellular infiltration is mild (Doig and Wood 1950) In comparing atrophic gastritis and gastric atrophy we may say that the mucosa is arranged in a regular pattern in gastric atrophy while it is haphazard in atrophic gastritis In accord with this *in gastric atrophy* the histamine test meal invariably reveal achlorhydria absence of pepsin and greatly diminished volume of secretion On several occasions *gastric biopsy has been of* value in determining the presence or ab ence of the subacute combined degeneration of the cord in patients with ob cure nervous lesions but *with no detectable* abnormality in the peripheral blood or bone marrow (Doig Motteram Robertson and Wood 1950) It has also been of value when liver *therapy has been given* to cases of anaemia before an adequate blood examination has been performed

SUMMARY

Gastric biopsy using the flexible biopsy tube has enabled us to make the following studies

(1) To establish the presence of superficial or atrophic gastritis and to investigate *its aetiology* symptomatology course and prognosis—this may be of importance as the disease is not infrequently mistaken for cancer of the stomach

(2) *To study the changes* in the gastric mucosa associated with pernicious anaemia and subacute combined degeneration of the spinal cord and to observe the effects of treatment Serial biopsies have also led *us to the belief that* liver therapy causes no regeneration of the gastric mucosa even after many years of treatment (Doig and Wood 1950)

(3) To study the relationship between the secretions of the gastric mucosa and its morphology It has been found that there is a direct correlation between atrophy and the volume concentration of free acid and pepsin content of gastric secretion following histamine stimulation

(4) To study the effects on the gastric mucosa of damaging agents such as alcohol and deep x ray therapy (Doig Funder and Weiden 1951) The latter has been used in the treatment of duodenal ulcer following the work of Ricketts and others (1948) in America

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REFERENCES

Benedict E B (1948) *Gastroenterology* **11** 281
Doig R K (1949) *Proc R Aust Coll Phys* **10** 85
— Funder J F and Weiden S (1951) *Med J Aust* **1** 828
— and Motteram R (1950) *Aust N Z J Surg* **19** 296
— — Robertson E G and Wood I J (1950) *Lancet* **2** 836
— and Wood I J (1950) *Med J Aust* **2** 565
Einhorn M (1894) *Med Rec N Y* **45** 780
Gunter G S (1950) *Gastroenterology* **15** 708
Hawksley J C (1939) *J Path Bact* **49** 585
— and Gooray G H (1948) *Ibid* **60** 333
Jackson C and Jackson C L (1935) *J Amer med Ass* **104** 269
Kenamore B Scheff H and Womack N A (1946) *Arch Surg Chicago* **52** 50
Motteram R (1951) *J Path Bact* **63** 389
Ricketts W E Palmer W L Kirsner J B and Hamman A (1948) *Gastroenterology* **11** 789
Schindler R (1937) *Gastroscopy The Endoscopic Study of Gastric Pathology* Chicago Illinois University of Chicago Press
Weiden S and Funder J F (1952) *Med J Aust* In press
Wood I J Doig R K Motteram R and Hughes A (1949) *Lancet* **1** 18
— — — Weiden S and Moore A (1949) *Gastroenterology* **12** 949

CHAPTER 16

PEPTIC ULCER

SECTION I

ENDEMIOLOGY

RICHARD DOLL

INTRODUCTION

THE CONVENTIONAL description of a group of ulcerative conditions of the intestinal tract under the generic head of peptic ulcer has its uses but also its dangers The term implies that the ulcers are all associated with exposure to pepsin and hydrochloric acid but it does not mean that they are produced in an identical manner Peptic has specifically been excluded from the heading of the section because epidemiological differences between gastric and duodenal ulcers are great One type of peptic ulcer almost disappears at a period when the prevalence of another greatly increases and one type may be common in one part of the world while it is rare in another part Moreover one aetiological factor does not always play the same part in both sexes nor at all ages It is probably also necessary to differentiate between acute and chronic ulcers The distinction used to be considered important but with the general use of radiography it has largely been forgotten and ulcers have been described as proven (by operation or by radiography) and clinical Now with the advent of gastroscopy it is recalled that there is a group of acute ulcers which heal and relapse but which rarely become chronic and for which independent aetiological factors may well be responsible

It is not always possible in the field of endemiology to divide ulcers into so many groups according to site and chronicity and according to the sex and age of the subject It is indeed rarely practicable to separate acute and chronic ulcers but whenever any sharpness of detail is required (as it must be when causes are uncertain) it is important to consider peptic ulcers separately in each of the other categories In particular it is essential to differentiate gastric and duodenal ulcers in men and in women

PREVALENCE IN ENGLAND

Sources of material

Estimates of the prevalence of a disease can be made from autopsy examinations from national mortality statistics from hospital series and from population surveys all the methods are open to criticism and the evidence obtained from the different sources is not infrequently contradictory Mortality statistics provide unsatisfactory evidence about the prevalence of a disease with a low fatality rate and changes in prevalence are likely to be confused by changes in fatality

moreover the diagnosis of cause of death is not always firmly established Hospital series are dependent on so many factors determining the selection of cases that they require great care in interpretation and the same applies to autopsy examinations A population survey is the method of choice for determining the prevalence of a chronic disease provided that the group chosen for survey can be considered typical of the general population

Autopsy series

Autopsy evidence of the incidence of peptic ulcer in Britain is surprisingly sparse Hurst and Stewart s (1929) series is the only large one to have been published but as there is reason to believe that the incidence of both gastric and duodenal ulcer has altered since the period when the material was collected the findings are not of immediate relevance

Population survey

Doll Avery Jones and Buckatzsch (1951) have recently conducted a survey of 5 951 persons most of whom lived in London The proportions of men and women in the main age groups who were found to have a peptic ulcer or to have had one in the past are shown in Table I The proportions in men are also shown separately for gastric and duodenal ulcer and for peptic ulcer of undetermined site *The last group contains some ulcers which were proved radiographically or* by operation but in which evidence of the exact site could not be obtained it also contains some diagnosed clinically on the symptoms alone The incidences given for gastric and duodenal ulcers are therefore too low and the gastric duodenal ratios correspondingly uncertain The number of ulcers observed in women was unfortunately too small to allow of any meaningful subdivision into sites

TABLE I

INCIDENCE OF PEPTIC ULCER IN MEN AND WOMEN AND OF KNOWN *GASTRIC AND DUODENAL ULCERS IN MEN*

Age in years	Men					Women	
	Number examined	Per cent incidence of ulcers				Number examined	Per cent incidence of peptic ulcer
		Gastric	Duodenal	Site unknown	Peptic total		
14 19	199	0 0	0 5	0 0	0 5	133	0 0
20–24	300	0 0	1 3	1 4	2 7	179	0 9
25–34	1 128	0 4	1 8	1 2	3 4	266	
35–44	1 375	1 4	4 1	1 5	7 0	236	2 0
45–54	1 089	2 8	3 9	2 9	9 6	167	
55–64	625	1 9	3 7	3 4	9 0	82	6 1
65 and over	155	1 9	3 2	2 6	7 7	17	

In men the incidence of peptic ulcer of all kinds was found to rise to a maximum little short of 10 per cent in the age group 45 54 years in women the highest incidence was 6 per cent and was not found until after the age of 55 years This

estimate for women must be accepted with considerable caution as the number of women examined was small moreover the incidence in the oldest age group partly reflects the great frequency of gastric ulcers among girls at the beginning of the century

If it is assumed that the age and sex incidences recorded in Table I are applicable to the whole of England and Wales it can be calculated that 5 8 per cent of men and 1 9 per cent of women between the ages of 14 and 64 years suffer or have suffered from a peptic ulcer Similarly it can be estimated that 971 000 men and 478 000 women in England and Wales of all ages have or have had ulcers This estimate of a total of 1 449 000 persons out of a population of 42 850 000 in 1946 compares with an estimate of 1 500 000 made by Avery Jones and Pollak (1945) on the basis of hospital experience and the national death rates for 1938

The relative proportion of gastric and duodenal ulcers encountered varied with age In the age groups 25–34 years the gastric duodenal ratio for men was 1 4 but above the age of 45 years it was more than 1 2

Not all the ulcers observed in the survey were active Some had been removed surgically and others had become quiescent in the course of time or as a result of medical treatment The proportion of active ulcers fell as age increased but 55 per cent of the men and women who had had ulcers were still having bouts of pain one or more times a year after the age of 55—a finding which indicates how unsatisfactory treatment still is

Hospital series

Hospital series are of value in providing information about the relative incidences of gastric and duodenal ulcers the relative incidences in men and women and the changes in incidence which occur over a period of time They are not appropriate for determining the actual incidences in the general population and the report that 9 per cent of adult general medical and surgical beds in hospitals are occupied by peptic ulcer patients does not indicate that 9 per cent of the population suffer from peptic ulcer Even the limited information obtainable from hospital series about relative incidences is open to major qualifications In the first place many series are confined to in patients and there is good reason to suppose that in patients are not representative of all ulcer patients attending hospital leave alone of all ulcer subjects Secondly paying patients tend to be under represented (which is important when social factors play a part in aetiology) and thirdly all cases attending are usually included instead of only those diagnosed for the first time in their lives

The most important civilian series recently published in England is that collected by Avery Jones and Pollak (1945) The figures relate to new cases diagnosed at the Central Middlesex Hospital London in 1943 and 1944 and both in patients and out patients are included The main findings are summarized in Table II For simplicity the group of 58 pyloric ulcers (46 in men and 12 in women) are combined with the duodenal ulcers Some of them were doubtless pre pyloric and should properly be classified as gastric ulcers but most authorities classify pyloric ulcers as duodenal (which in fact most prove to be) and it is better to follow the rule in order to facilitate comparisons with other series

TABLE II

NUMBER OF CASES OF GASTRIC AND DUODENAL ULCER WITH GASTRIC DUODENAL AND SEX RATIOS (CENTRAL MIDDLESEX HOSPITAL LONDON 1943-44)

Age in years	Number of gastric ulcers		Number of duodenal ulcers		Gastric duodenal ratio		Sex ratio	
	Male	Female	Male	Female	Male	Female	Gastric	Duodenal
10-24 –	2	1	24	10	1 12 0	1 10 0	2 0 1	2 4 1
25-34 –	12	9	148	22	1 12 3	1 2 4	1 3 1	6 7 1
35-44 –	49	18	176	26	1 3 6	1 1 4	2 7 1	6 8 1
45-54 –	61	20	127	18	1 2 1	1 0 9	3 1 1	7 1 1
55-64 –	52	23	75	10	1 1 5	1 0 4	2 3 1	7 5 1
65 and over	16	8	40	5	1 2 5	1 0 6	2 0 1	8 0 1
All ages above 10	192	79	590	91	1 3 1	1 1 2	2 4 1	6 8 1

From Table II it is seen that the gastric duodenal ratio changes with age in both sexes whereas the sex ratio is relatively constant for each site irrespective of age An interesting feature of the series is the inclusion of 42 acute gastric ulcers which were diagnosed gastroscopically The numbers are of course small but the observation that men and women were equally affected in this group supports the suggestion that the acute ulcer is different aetiologically from the common chronic ulcer

Mortality statistics

The Registrar General s mortality figures give a rather different picture Table III shows the deaths reported from gastric and duodenal ulcer in England and Wales in 1947 the figures are set out in the same way as in Table II for ease of comparison

TABLE III

NUMBER OF DEATHS DUE TO GASTRIC AND DUODENAL ULCER WITH GASTRIC DUODENAL AND SEX RATIOS (ENGLAND AND WALES 1947 REGISTRAR GENERAL)

Age in years	Deaths due to gastric ulcer		Deaths due to duodenal ulcer		Gastric duodenal ratio		Sex ratio	
	Male	Female	Male	Female	Male	Female	Gastric	Duodenal
10-24 –	11	6	12	2	1 1 09	1 0 33	1 8 1	6 0 1
25-34 –	43	10	67	7	1 1 56	1 0 70	4 3 1	9 6 1
35-44 –	208	36	205	16	1 0 99	1 0 44	5 8 1	12 8 1
45-54 –	436	104	357	30	1 0 82	1 0 29	4 2 1	11 9 1
55-64 –	595	189	456	44	1 0 77	1 0 24	3 2 1	10 0 1
65 and over	838	501	518	155	1 0 62	1 0 31	1 7 1	3 3 1
All ages above 10	2 131	846	1 615	254	1 0 76	1 0 30	2 5 1	6 4 1

Comparison between results from different sources

In contrast to the hospital series the mortality figures show a steady increase with age the greatest number of deaths occurring in the over 65 year age group while the maxima in the hospital series are between 45 and 64 years for gastric ulcers and between 35 and 44 years for duodenal ulcers This difference is readily explained by the far greater fatality of peptic ulcers in the higher age groups Differences in the gastric duodenal ratio are also partly attributable to differences in fatality Haemorrhage or perforation of a gastric ulcer is a more dangerous condition than a similar complication of a duodenal ulcer and this necessarily results in the gastric duodenal ratio being greater when calculated from deaths than when calculated from live subjects If it is assumed that gastric ulcer is two and a half times as fatal as duodenal ulcer and the number of duodenal deaths accordingly multiplied by 2 5 a reasonable similarity is obtained between the material from the three sources which have been referred to previously The figures concerned are set out in Table IV

TABLE IV

GASTRIC DUODENAL RATIOS OBTAINED FROM DIFFERENT SOURCES

Age in years	Gastric duodenal ratio: Men — Population survey* (1946-47)	Men — Hospital series (1943-44)	Men — D aths (1947 duodenal × 2 5)	Women — Hospital series (1943-44)	Women — Deaths (1947 duodenal × 2 5)
10-24 - -	0 5	1 12 0	1 8	1 10 0	1 0 8
25-34 - -	1 4 0	1 12 3	1 4 0	1 2 4	1 1 8
35-44 - -	1 3 0	1 3 6	1 2 3	1 1 4	1 1 0
45 54 -	1 1 4	1 2 1	1 7 0	1 0 9	1 0 8
55 64- -	1 1 9	1 1 5	1 2 0	1 0 4	1 0 5
65 and over	1 1 7	1 5	1 1 5	1 0 6	1 0 8
All ages	1 2	1 3 1	1 2 0	1 1 ?	1 0 8

C l l t d f m the absol t mber bse d n t fr m th pp m t p ge g n n T bl II

The only gross disparity is in the hospital series which shows a much higher proportion of duodenal ulcers in the younger age groups

In a similar way the differences between the sex ratios in the hospital and death registration series can be interpreted as signifying that gastric and duodenal ulcers are between one and a half and two times as fatal in men as in women The survey figures unfortunately do not provide sufficient female cases for useful analysis

PREVALENCE IN SCOTLAND

Very different figures have been reported from Scotland Jamieson Smith and Scott (1949) have recorded details of all the ulcer patients attending the Western

Infirmary Glasgow between 1 May 1946 and 30 April 1948 *Their findings are* summarized in Table V

TABLE V

GASTRIC DUODENAL RATIO IN MEN AND WOMEN AND SEX RATIOS OF GASTRIC AND DUODENAL ULCERS (WESTERN INFIRMARY GLASGOW 1 5 46–30 4 48)

Age in years	Gastric duodenal ratio		Sex ratio	
	Male	Female	Gastric	Duodenal
10–24	1 35 0	1 7 2	0 7 1	3 2 1
25–34	1 13 4	1 17 6	5 3 1	4 0 1
35–44	1 11 5	1 5 7	2 0 1	4 1 1
45–54	1 7 6	1 4 1	2 2 1	4 1 1
55–64	1 5 4	1 2 7	1 8 1	3 6 1
65 and over	1 5 2	1 1 2	0 7 1	3 3 1
All ages above 10	1 9 5	1 4 5	1 8 1	3 9 1

Comparison of Tables II and V shows some important differences At nearly *all ages and in both sexes the ratio of duodenal to gastric ulcers is from 3 to 4* times higher in Glasgow than in London and the proportion of female cases is *higher at both sites Mortality figures for Scotland in 1947* agreed in showing a higher proportion of duodenal deaths than in England and indicated that this was *partly due to an excess of duodenal ulcers but that it was also partly contributed* to by a deficiency of gastric ulcers

On the other hand the figures did not show any difference between the mortality rates for women between Scotland and England The relevant mortality rates *per 1 000 000 population are shown in Fig 164*

CHANGES IN PREVALENCE IN GREAT BRITAIN

Hospital series

Improvements in diagnostic technique have made it impossible to compare the prevalence of uncomplicated ulcers as recorded by clinical series at different periods nor can great reliance even be placed on the sex and site ratios *On the* other hand perforation and haemorrhage are such dramatic complications of an ulcer that their recognition is comparatively *independent of modern refinements* in diagnosis and it is reasonable to compare the clinical experience of these complications *over the years*

According to Jennings (1940) perforations only came to be mentioned in the *literature at all frequently at the beginning of the nineteenth century* and at that time they were invariably reported in young women In the second half of that *century perforations* near the cardia became common when 3 out of every 6 occurred in women under 25 years of age 1 occurred in an older woman and *only* 2 were in men Since 1920 9 out of 10 perforations have occurred in men and the tenth has been in a middle aged woman

A similar change has taken place in the age and sex distribution of cases of haematemesis According to Avery Jones (1947) nearly 50 per cent of the cases before 1910 occurred in women under 40 years of age Now this group is responsible for only 5 per cent and the majority of cases are in men

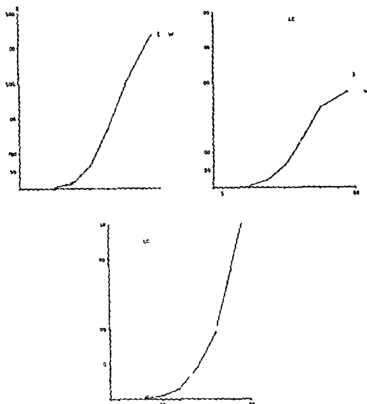


Fig 164 —Mortality from gastric and duodenal ulcer in England Scotland and Wales 1947 (death rate per 1 000 000 living)

These proportional changes undoubtedly reflect changes in incidence Perforations in young women disappeared as common events soon after the turn of the century perforations in men have greatly increased It is moreover notable that the great majority of perforations in men are now recorded as being in the juxtapyloric region For example Illingworth Scott and Jamieson (1944) found that admissions for perforated ulcer to the Western Infirmary Glasgow increased sixfold between 1910 and 1940 They were able to estimate that the annual incidence per 100 000 population doubled between 1924 and 1934 and the increase was entirely due to an increase of juxtapyloric ulcers in men

Mortality statistics

Deaths attributed to gastric and duodenal ulcers have shown marked variations in England and Wales in the last 50 years In the earlier part of the century the diagnoses must have been to some extent less precise and duodenal ulcer was not shown separately as a cause of death till 1921, but this cannot be the explanation of the more recent changes The trends since 1921 are shown in Fig 165

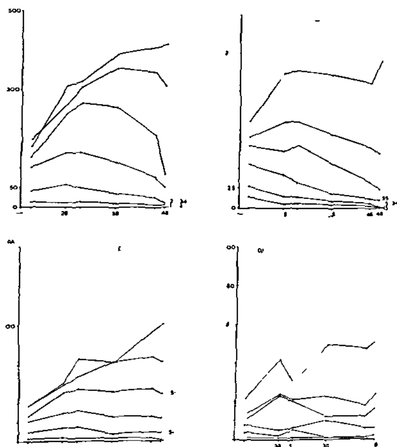


FIG 165 —Trends of mortality (in each age group) from gastric and duodenal ulcer England and Wales 1921–48 (death rates per 1 000 000 living)

The graphs show clearly the necessity for considering ulcers separately at each site in each sex and in the main age groups The death rate from gastric ulcer in men increased rapidly between 1921 and 1931 the age group of 45 years and above being particularly affected After 1931 the death rate began to fall at all ages below 55 years and it has fallen rapidly since World War II above 55 years of age the increase has gradually faded out and the death rate would now appear to be constant if it is not also falling The death rate from duodenal ulcer in men showed a less steep increase between 1921 and 1931 since then it

has maintained its level at all ages below 55 years and has continued to rise in the higher age groups The changes in women have approximately paralleled the changes in men save that there has been a steady decrease throughout in the death rate from gastric ulcers at all ages under 45 years and the increase in the period 1921–31 occurred to an appreciable extent only among women over 65 years of age

It does not seem possible to explain the rise in death rates between 1921 and 1931 by changes in methods of diagnosis or of certification so that the sharp increase in mortality from both gastric and duodenal ulcers at the upper ages in both sexes must be ascribed to an increased prevalence Since 1938 there has been a sharp decrease in the fatality rate of cases of peptic ulcer and much if not all of the fall in mortality from gastric ulcer can be attributed to improved treatment There is no reason to suppose that improvements in treatment have not affected duodenal ulcers to a similar extent so that the practically unchanged mortality from duodenal ulcer must mask an actual continued rise in prevalence

PREVALENCE IN OTHER COUNTRIES

Countries of European culture

The major part of this section is devoted to British figures because so many variables enter into the interpretation of statistics from different countries that it is difficult to make useful comparisons between them Broadly it may be said that peptic ulcer is a common disease in all countries of European culture and that changes in sex and site distribution have taken place similar to those which have occurred in Britain Jennings (1940) concluded that perforations in young women ceased to occur at all commonly at the beginning of this century in Germany France and Scandinavia as well as in the English speaking countries A little later Bager (1929) found a steady increase in the number of admissions for perforated ulcer in Sweden He collected 1 495 cases treated at 50 hospitals

TABLE VI

CHANGE IN PREVALENCE OF PEPTIC ULCER AND SEX RATIO IN DENMARK 1901–35

Period	Hospital series (Copenhagen)		Mortality statistics (Denmark)	
	Number of cases	Sex ratio M F	Number of cases	Sex ratio M F
1901–05	471	0·3 1	—	—
1906–10	652	0·5 1	—	—
1911–15	964	0·9 1	282	0·9 1
1916–20	1 249	1·0 1	373	1·1 1
1921–25	1 493	1·8 1	677	1·6 1
1926–30	1 793	2·7 1	766	2·2 1
1931–35	2,559	3·1 1	1 193	2·8 1

during the period 1911–25 and found that the number treated in the third 5 year period was three times as great as in the first Moreover like Illingworth in Scotland he found that the increase was entirely due to an increase of juxtapyloric perfora tions in men

Hansen (1937) has demonstrated very clearly the reversal of the sex ratio which took place in Denmark He analysed the records of both in patients and out patients in Copenhagen and compared them with mortality statistics His findings are summarized in Table VI

The records of the Metropolitan Life Insurance Company of New York are of interest as showing the increase in duodenal ulcer in men which has taken place as well as the decrease in gastric ulcer in women Table VII is modified from a Table given by Ivy Grossman and Bachrach (1950)

TABLE VII

MORTALITY FROM GASTRIC AND DUODENAL ULCER
METROPOLITAN LIFE INSURANCE COMPANY
(RATES PER 100 000)

Period	Mortality from			
	Gastric ulcer		Duodenal ulcer	
	Men	Women	Men	Women
1911–15	5 5	3 2	*	*
1921–23	4 9	1 9	1 8	0 6
1931–33	6 5	1 5	3 0	0 5
1941–43	6 7	0 9	3 1	0 5

D ths f m duodenal ulcer wer not record d p ately fr m other d seases of stom h d duod m

The only population survey which is comparable to the recent English one is that recorded by Knutsen and Selvaag (1947) in Norway Their results are based on claims for special rations in the town of Drammen during the German occupation The diagnoses given on the certificates issued during 1942 were checked after World War I against barium meal reports and the figures are considered to represent a close estimate of the total incidence in the town Altogether 556 peptic ulcers were found among 21 918 men and women over the age of 15 years The maximum incidence of 6 1 per cent was found in men aged 40–49 years and this compares very closely with the maximum incidence of active ulcers of 6 0 per cent found by Doll Avery Jones and Buckatzsch in men of 45–54 years The higher figure of 9 6 per cent obtained in the English series includes ulcers no longer active and must provide a less suitable comparison

Despite the broad similarities there remain a number of differences in detail Table VIII shows the sex and site ratios reported in a number of recent series from different countries

TABLE VIII

GASTRIC DUODENAL AND SEX RATIOS REPORTED FROM DIFFERENT COUNTRIES

Country	Authority	Period	Number in series	Gastric duodenal ratio		Sex ratio M	F
Sweden	Ihre and Muller (1943)	1930-40	1 193	1	4 2	2 5	1
Switzerland	Mirault Kretchmar (1945)	1939-44	2 522	1	1 3	3 6	1
England	Avery Jones and Pollak (1945)	1943-44	957	1	3 1	4 7	1
N Norway	Schanke (1946)	1941-44	232	1	0 4	3 3	1
Belgium	Hillemand and Sarrazin (1946)	1943-45	1 001	1	2 7	4 1	1
Australia	Linn (1946)	1939-44	1 077	1	1 6	7 0	1
Norway	Knutsen and Selvaag (1947)	1942	566	1	2 2	2 4	1
U S A	Eusterman (1947)	1941-45	—	1	1 5	3 6	1
Scotland	Jamieson Smith and Scott (1949)	1946-48	3 258	1	7 7	3 5	1

Ir pat ts o ly

The series quoted from the United States of America comes from the Mayo Clinic and must therefore be presumed to relate to a somewhat selected economic class it is in sharp contrast to the mortality figures given by the Metropolitan Life Insurance Company which have been cited above in Table VII and which closely resemble English mortality figure Other big contrasts are seen in the reports from central and northern Norway and from England and Scotland It is therefore very difficult to assess the significance of geographical factors when social factors within one country can be seen to produce as great differences as those reported between distant countries

Countries of African and Asiatic culture

Outside Europe it is less easy to obtain detailed figures but there is enough evidence to show that peptic ulcers are far from being the prerogative of any one race In the United States of America in 1940 (U S Public Health Service 1947) the mortality from peptic ulcer among white males was 11 3 per 100 000 among other males (mostly Negro) it was 9 6 among white females it was 2 3 and among other females it was 3 3 On the other hand Eagle and Gillman (1938) found a much lower incidence of peptic ulcer at autopsy among the Bantu of South Africa than among Europeans (0 4 per cent against 3 per cent) It would seem significant that the Negro in the United States of America lives under conditions of life essentially similar to those of the poorer class of white Americans while his conditions are basically different in South Africa In contrast to both these experiences Ellis (1948) found that a peculiar stenosing form of duodenal ulcer was common among Nigerians In his series there were 125 duodenal ulcers and only one gastric ulcer

There have been reports that peptic ulcer is common in many parts of Asia including Japan and China and duodenal ulcer is one of the most important diseases in Southern India (Somervell and Orr 1936) A particularly interesting report about peptic ulcer in Java has been made by Kouwenaar (1930) He found

that gastric and duodenal ulcers were common among the Chinese one or other being present in as many as 10 per cent of autopsies but that peptic ulcer was found in only 1 per cent of autopsies on the Javanese With the exception of a slightly greater consumption of meat and a greater use of animal fats in cooking by the Chinese he considered that both groups lived in similar environments and had similar habits Most of the Chinese were however immigrants and may have been exposed to other conditions in their youth It is to be hoped that further studies will be made in Java as such a gross difference in incidence between two closely associated communities may well furnish an important key to the fundamental causes of the condition

DIFFERENCES BETWEEN TOWN AND COUNTRY

As has been shown appreciable differences exist between the incidence of gastric and duodenal ulcers in different countries even when the inhabitants are as closely similar as they are in England and Scotland It is therefore not surprising to find that differences exist in different cultural groups within a country One of the simplest ways of dividing the inhabitants of industrialized nations is into town and country dwellers that is according to the density of population With one exception the incidence of peptic ulcer has always been reported as being lower in countrymen than in townsmen The exception is Schanke s (1946) report from northern Norway but here the towns were small and the countrymen were mainly employed in fishing an occupation which showed a specifically high incidence of gastric ulcer

Morris and Titmuss (1944) analysed the Registrar General s records for 1928–30 and found that the death rate from gastric ulcer in men over the age of 35 years was approximately 100 per cent higher in London than in rural areas in women the increase was less marked and became apparent only after the age of 45 years Rather surprisingly the mortality from duodenal ulcer showed less fluctuation

TABLE IX

MORTALITY FROM PEPTIC ULCER ACCORDING TO DENSITY OF POPULATION 1948
(DEATH RATES PER 100 000 LIVING)

Type of ulcer	Density of population	Men: Age in years 15–44	Men: Age in years 45–64	Men: Age in years 65+	Men: All ages	Women: Age in years 15–44	Women: Age in years 45–64	Women: Age in years 65+	Women: All ages
Gastric ulcer	Greater London	3	25	60	12	0	4	25	4
	County boroughs	3	26	47	11	0	5	18	3
	Urban districts	2	20	38	10	0	4	18	3
	Rural districts	1	18	29	8	0	5	15	3
Duodenal ulcer	Greater London	2	15	43	8	0	2	7	2
	County boroughs	3	18	29	8	0	2	4	1
	Urban districts	4	17	27	8	0	0	6	1
	Rural districts	2	11	25	6	0	1	3	1

There was a marked excess in London in men over the age of 55 years but the graduation was generally less clear the figures for women were too small for any definite conclusions to be drawn Since then the differences have become less marked Death rates per 100 000 for the various density of population groupings for 1948 are shown in Table IX There is very little difference below the age of 65 years above that age the difference is still appreciable and is greater for gastric ulcers than for duodenal ulcers and for men than for women

An objection which has been raised to these figures as well as to the reports from other countries is that the standard of diagnosis may be poorer in the country and more cases may consequently be missed This is almost certainly part of the explanation of some of the differences reported (for example Ginanneschi 1938) but it is unlikely to be the whole explanation In England Doll Avery Jones and Buckatzsch (1951) found that agricultural workers had only 41 per cent of the number of ulcers expected from the experience of the total number of men examined and there was no excess of men with ulcer symptoms who had previously escaped diagnosis the number of men with frank complications (haemorrhage and perforation) was also less than was expected It is of some interest that the low incidence of peptic ulcer was found among agricultural workers only and not among country dwellers generally

The difference in incidence between townsmen and countrymen has been held to support the belief that the character of modern civilization is to blame for the increased incidence of ulcer according to Bockus (1943) ulcer is a civilization disorder and as the complexities of life increase one may anticipate an even greater incidence of peptic ulcer If this is so it must be accepted that the complexities of life have spread comparatively evenly throughout England in the last 20 years

SOCIAL CLASS DIFFERENCES

Another way of subdividing a community is by social class The Registrar General divides the adult population into five big classes according to occupation and the classification corresponds roughly with economic status The classes are defined in outline as follows (the percentage of the male population falling into each class are shown in parantheses)

(1) Leading professions such as directors of companies (2 5 per cent)
(2) Lesser professions such as employers and managers in industry transport trade (14 0 per cent)
(3) Skilled workers including clerks and salesmen (49 2 per cent)
(4) Semi skilled workers including most agricultural workers (17 8 per cent)
(5) Unskilled labourers (16 5 per cent)

At the time of the 1931 census little difference between the social classes was recorded by the Registrar General in the mortality from duodenal ulcer but there was found to be a sharp increase in the mortality from gastric ulcer in men with descent in the social scale The same result was obtained by Doll Avery Jones and Buckatzsch (1951) in the morbidity survey of the population previously referred to Both series of results are shown diagrammatically in Fig 166 In comparing different social classes it is necessary to take age into consideration and the results are therefore expressed as standardized mortality and morbidity ratios

The standardized ratios are obtained by expressing the observed number of deaths (or cases) in each social class as a percentage of the expected number The expected numbers are calculated from the experience of all social classes each age group being taken separately

From Fig 166 it is seen that gastric ulcer is between 2 and 5 times as prevalent in the poorest class as in the upper social classes

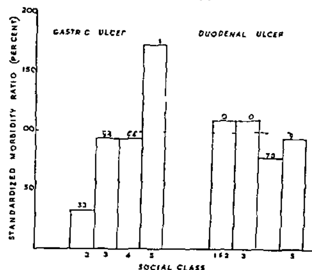
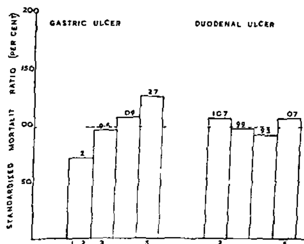


Fig 166 —Social class incident of gastric and duodenal ulcer Results obtained from a population survey and from the Registrar General s mortality figures



Morris and Titmuss (1944) *made a more detailed study of the class factors* affecting ulcer mortality and they found that above the age of 65 years there was an increased mortality in the upper social classes particularly marked in the case of duodenal ulcer There are however fallacies in the assessment of social class by means of occupation after retiring age and the finding requires further investigation Meanwhile *the agreement of mortality and morbidity studies on the working*

population provides a strong reason for concluding that an environmental factor associated with poverty plays an important part in the production of gastric ulcers

OCCUPATIONAL DIFFERENCES

The literature on occupational differences in the incidence of peptic ulcer is conflicting In the nineteenth century it was commonly stated that cooks and bootmakers were the most frequent sufferers the theory was that cooks injured their stomachs by the continual tasting of hot foods while bootmakers injured theirs by pressure against the boots on which they were working It is not now possible to determine the truth of these statements for the time when they were made but it is certain that they are not applicable to modern times

A multitude of reports have suggested that high incidences are characteristic of many occupations but the very multiplicity of occupations suggests that the evidence is not strong In no case can it be maintained that ulcer is a specific industrial hazard of the occupation though the suggestion has frequently been made with regard to busmen Busmen themselves have been so convinced that they suffered unduly from the broad group of digestive diseases that the Industrial Health Research Board invited Bradford Hill to investigate the situation The results indicated that busmen did suffer from digestive diseases more than tram workers but no information was obtained specifically about peptic ulcer (Hill 1937)

Despite the different results obtained by different workers a general pattern of *agreement can be discerned High incidences are thought to be characteristic of* doctors executives transport workers and fishermen and low incidences to be characteristic of agricultural workers and clerks The evidence is strongly suggestive in the case of doctors but it must be remembered that the criteria of diagnosis used in medical men differ from those used in the general public A doctor may obtain a barium examination much more readily than a member of another profession and he is more likely to recognize the significance of a small melaena and to have it investigated Both in Britain and the United States of America the mortality of doctors from peptic ulcer is similar to that of comparable sections of the community and it is reasonable to attribute the diagnosed excess to an excess of diagnosis If however there is a real excess it is entirely confined to duodenal ulcers

The position is different with regard to fishermen and agricultural workers In both instances the evidence is sufficiently strong to be regarded as proof Schanke s *(1946) observations on fishermen are of particular value as they provide the only* known example of an occupational group with a clear excess of gastric ulcers According to his calculations the incidence of gastric ulcers among fishermen was 1 9 times that among the rest of the population In contrast the incidence of duodenal ulcers was only 1 1 times higher Agricultural workers have always been reported as having a low incidence of peptic ulcer but there has been the objection that the low incidence might be the result of inadequate diagnosis in the countryside and so be more apparent than real This objection as has been mentioned previously can no longer be upheld and it must be accepted that peptic ulcers (probably in both stomach and duodenum) are relatively less common among agricultural workers

The survey by Doll Avery Jones and Buckatzsch (1951) provides the most recent evidence on occupational differences The results are summarized in Table X

TABLE X

INCIDENCE OF PEPTIC ULCER AMONG MEN EMPLOYED IN DIFFERENT OCCUPATIONS

Occupational group	Number of men examined	Number of men found to have peptic ulcers	Number of men expected to have peptic ulcers
Doctors	127	15	6.9
Unskilled workers (unclassified)	64	11	4.7
Foremen	253	27	19.7
Business executives	98	11	7.1
Skilled engineering tradesmen	595	37	33.9
Semi skilled engineering workers	298	21	18.7
Bus and trolleybus drivers	395	32	30.0
Skilled workers (unclassified)	227	16	15.2
Research workers (professional)	200	9	9.2
Lorry drivers	128	12	12.6
Semi skilled workers (unclassified)	236	15	16.3
Heavy manual workers (unskilled)	650	43	45.2
Clerks	342	20	21.7
Heavy manual workers (semi skilled)	129	9	10.2
Horse vehicle drivers	77	5	6.4
Waiters	126	5	7.9
Bus and trolleybus conductors	269	12	16.7
Higher civil servants	143	8	13.0
Social classes 1 and 2 (unclassified)	261	3	8.2
Agricultural workers	203	5	12.2

The high incidence among doctors and the low incidence among agricultural workers have already been commented on The high incidence among the unclassified unskilled workers is considered to be an artefact due to men having taken no sheltered occupations because of having an ulcer The high incidence among men holding managerial posts in industry and among foremen is thought to be real and is of considerable interest The excess ulcers in this group were all duodenal and this can be related to the finding that men with duodenal ulcers complained disproportionately of anxiety arising from their work The survey entirely failed to substantiate the existence of any abnormal prevalence of ulcers *among bus or lorry drivers or among bus conductors nor could any excess of* ulcers be found among men working shifts or at night The authors concluded that *the survey has provided clear proof of the prevalence of gastric and duodenal* ulcers in the general population but less variation of incidence has been found *than might have been expected if conditions of work played an important role* in the genesis of the disease

PREVALENCE IN ANIMALS

Peptic ulcer is characteristically a disease of humans but it is not unknown among other animals domestic and wild Individual chronic ulcers have been reported by veterinary surgeons in monkeys cattle horses swine and dogs The site has

almost always been in the stomach but Overgaard (1934) in Copenhagen found three duodenal ulcers in the course of autopsies on 1 000 dogs

In two species of animals gastric ulcers are common Acute mucosal lesions are almost universal in the stomachs of young calves weaned before they have developed the capacity to ruminate and chronic ulcers have been observed is frequently as in 2-5 per cent of instances (Bongert 1912) Seals off the lower Californian coast provide the other example Schroeder and Wegeforth (1935) found gastric lesions including chronic indurated ulcers and scars in all of 46 animals Nematode worms were invariably found infesting the ulcers but it would seem more reasonable to attribute the development of the ulcers to the ingestion of the hard sharp stones which are habitually swallowed after a meal by seals in this district In other parts of the world where the stones are less hard and where nematode infestation is also less common ulcers are not found In both these cases the primary factor is probably physical trauma the suggestion that early weaning may be responsible through the mechanism of psychological trauma is too far fetched to be entertained seriously

Experimentally acute ulcers can be produced in the stomach and duodenum of many species and chronic ulcers closely resembling those found in humans can be produced by short circuiting operations and by the injection of histamine in bees wax *It is not therefore safe to conclude that the greater prevalence of peptic* ulcer in humans is a true species difference other animals are susceptible and the difference may as readily be attributable to habits which are the concomitants of human civilization

SUMMARY AND CONCLUSIONS

Peptic ulcer is a generic name for a group of conditions which are in many respects endemiologically different Whenever possible peptic ulcers should be considered separately according to site and chronicity and according to the sex and age of the subject

In Britain gross changes in the prevalence of the different types of ulcer have taken place in the last 50 years Gastric ulcer in young women which used to be very common at the beginning of the century has now become rare This is in such marked contrast to other types that there must have been some special agent responsible for their development which is no longer operative Gastric ulcer in men became more frequent after World War I and so to a lesser extent did gastric ulcer in older women since 1931 the incidence in both these groups has remained stationary or decreased Duodenal ulcer became more frequent at about the same time but its prevalence has continued to increase and has probably not yet reached its maximum the trends in men and women have been *similar though the incidence in women has been much lower*

Peptic ulcer becomes more frequent as age advances and in England is found in nearly 10 per cent of men aged 45-54 years In life duodenal ulcer is found 4 or more times more often than gastric under the age of 35 years but after 45 years it is only 1 or 2 times as common Gastric ulcers are 2-3 times commoner in men than in women and duodenal ulcers are 6-12 times commoner at least at all ages between 25 and 65 years

In Scotland duodenal ulcers are commoner and gastric ulcers less common than in England other differences probably also exist but they have not been firmly established

Both types of ulcer are commoner in the big towns than in the country but the difference is only marked in the upper age groups and is clearer for gastric than for duodenal ulcers The difference has become less distinct in the last 20 years

Duodenal ulcer is equally common among all social classes but gastric ulcer is primarily a disease of the poorer economic grades Occupational differences are otherwise less marked than have been supposed An excess of duodenal ulcer can be observed among doctors and among men in responsible positions in industry the excess among doctors can reasonably be attributed to finer diagnosis Fishermen in northern Norway show an excess incidence of gastric ulcers and agricultural workers show a low incidence of peptic ulcers generally The evidence for a high incidence among transport workers is weak

The trends in other countries of European culture appear to have been similar but it is difficult to assess the significance of geographical differences when social factors within a country can cause such large variations Racial differences in susceptibility have not been established the African Negro may show a low incidence in South Africa but in the United States of America Negroes suffer from peptic ulcer much as do White Americans In Java there is a marked difference between the Chinese and the Javanese which may be of major aetio logical significance The frequency with which duodenal ulcer is found in Southern India and in Nigeria makes it difficult to attribute it principally to the tension and rush of industrial civilization

Peptic ulcer is uncommon in animals but gastric and more rarely duodenal ulcers have been found in several species Chronic gastric ulcers are common in calves weaned at birth and in seals caught off the Californian coast In both cases the origin is thought to be physical trauma

REFERENCES

Avery Jones F (1947) *Brit med J* 2 441 477
— and Pollak H (1945) *Ibid* 1 797
Bager B (1929) *Acta chir scand* 64 *Suppl* 11
Bockus H L (1943) *Gastroenterology* Philadelphia Saunders
Bongert J (1912) *Berl klin Wchnschr* 49 807
Doll R Avery Jones F and Buckatzsch M M (1951) *Med Res Counc Spec Rep Ser* No 276
Eagle P C and Gillman J (1938) *S Afr J med Sci* 3 1
Ellis M (1948) *Brit J Surg* 36 60
Eusterman G B (1947) *Gastroenterology* 8 575
Ginanneschi G (1938) *Med d Lavoro* 29 65
Hansen J (1937) *Ugesk Laeger* 99 1145
Hill A B (1937) *Med Res Coun Industr Health Res Bd Report* No 9
Hillemand P and Sarrazin (1946) *Acta gastro-enterol Belg* 9 134
Hurst A F and Stewart M S (1929) *Gastric and Duodenal Ulcer* London Oxford University Press
Ihre B J E and Muller R (1943) *Acta med scand* 116 33
Illingworth C F W Scott L D W and Jamieson R A (1944) *Brit med J* 2 617 655
Ivy A C Grossman M I and Bachrach W H (1950) *Peptic Ulcer* London Churchill
Jamieson R A Smith W E and Scott L D W (1949) *Brit med J* 1 298

REFERENCES

Jennings D (1940) *Lancet* 1 395 444
Knutsen B and Selvaag O (1947) *Acta med scand Suppl* 196 341
Kouwenaar W (1930) *Ned Tijdschr Geneesk* 74 23?
Linn H W (1946) *Med J Aust* 2 649
Mirault Kretchmar M (1945) *Gastroenterologia* 70 275
Morris J N and Titmuss R M (1944) *Lancet* 2 841
Overgaard K (1934) *Acta med scand* 81 429
Schanke K (1946) *Acta chir scand Suppl* 115
Schroeder C R and Wegeforth H M (1935) *J Amer vet med Ass*
Somervell T H and Orr I M (1936) *Brit J Surg* 24 227
U S Public Health Service (1947) *Vital Statistics rates in the United States* 1900–1940 Washington United States Government Printing Office

SECTION II

AETIOLOGY

W I CARD

THE cause of peptic ulcer is the digestion by acid and pepsin of the oesophageal gastric duodenal or *intestinal mucosa* Since acid and pepsin exist in stomachs which do not show ulceration there must clearly be some protective mechanism in the mucosa which resists digestion The inescapable equation of ulcer aetiology is therefore

(Acid + Pepsin) *versus* (Mucosal resistance)

ACID AND PEPSIN

The evidence that acid and pepsin are necessary for the formation of ulcers rests on secure foundations Ulcers are only found in those sites to which acid and pepsin have access that is the lower end of the oesophagus the stomach the duodenum at the anastomosis between the stomach and small intestine and occasionally in a Meckel s diverticulum which has functioning gastric mucosa Active peptic ulcers do not occur in a stomach with proved and persistent achlorhydria In order to prove achlorhydria the aspirating tube must be shown radiologically to lie in the stomach and only those who make a practice of screening know how frequently the tube may coil in the fundus the juice must be aspirated continuously the parietal cells must be stimulated by histamine of proved potency and if histamine produces no secretion insulin must be used as a stimulus and the blood sugar measured to ensure that adequate hypoglycaemia results If these criteria are adopted there will be found very few if any cases in the literature which show an active benign ulcer with achlorhydria Gastric ulcer has never been reported in a case of pernicious anaemia

If acid and pepsin are necessary for the formation of an ulcer it might be expected though it does not necessarily follow that prolonged achlorhydria would result in its healing Apart from the effects of gastrectomy the only procedure that has been employed to this end is the irradiation of the gastric mucosa with x rays *Ricketts and others (1949) have made careful studies* of this procedure and have shown that where radiation therapy produced prolonged achlorhydria healing of the ulcer always occurred Though acid secretion returned in some instances and might be accompanied by a recurrence of the ulcer recurrence never occurred in the presence of an achlorhydria

We may therefore take it as certain that acid and pepsin are necessary for ulcer formation They may be a necessary though not the efficient cause to borrow from

scholastic logic As between ulcer subjects and normals there are various possible differences in gastric secretory behaviour

(1) Gastric secretion is altered in quality

(2) Gastric secretion is altered in quantity in response to histamine stimulus or a meal

(3) Abnormal secretion continues in an otherwise resting stomach—the inter digestive phase

Gastric secretion—qualitative

Most investigators believe that the primary secretion of acid by the parietal cells occurs at a fixed concentration of approximately 160 mM strength and that there is in addition a diluting non parietal secretion It is the mixture of these two which produces the secondary acidity as measured in aspirated gastric juice quite apart from dilution with saliva foodstuffs or regurgitated duodenal juice Fisher and Hunt (1950) have analysed recently the figures of Ihre (1939) who has done careful work on human gastric secretion Making the arbitrary assumptions that these two secretions are iso-osmotic and that the common cation is 170 mEq l his results indicate that human parietal secretion contains 160 mEq l hydrion and 10 mEq l neutral chloride His analysis further shows that the composition of juice obtained from a series of ulcer subjects was also consistent with this hypothesis These relationships are in fact applicable not only to a selected group of normal men but to a group of gastric and duodenal ulcers and are consistent with the view that the quality of parietal cell secretion in normal and ulcer subjects differs in no way Hyperacidity in so far as it implies a higher primary acidity to be found in ulcer subjects or a higher secondary acidity using a histamine stimulus has no basis in experimental fact

Gastric secretion—quantitative

There is the second possibility that though parietal cell secretion is of identical composition in normal subjects and those with ulcers the stomach particularly in the case of duodenal ulcer subjects may be capable of producing larger acid outputs than normal or may do so with a standard submaximal histamine stimulus How may the maximal acid output of the stomach be measured ? If we make the assumption that there is a mean maximal output for each parietal cell then the total acid output of the stomach will be related to the total parietal secretory cell mass Though it is no possible to stimulate the human stomach maximally owing to the unpleasant side-effects of histamine it is possible by giving constant intra venous doses of histamine and measuring the corresponding acid outputs to construct a dose response curve The maximal or limiting output may then be obtained by extrapolation (Adam and others 1951) The dose response curve is of sigmoid shape and may be fitted to a probability integral curve for which a hypothetical basis can be put forward of a population of parietal cells the secretory cell mass containing cells with a varying sensitivity to histamine Whatever the exact interpretation of this curve it has two important parameters the intravenous dose of histamine that gives the half-output response and the maximal or limiting output of the stomach It is the latter which should be related to the secretory cell mass The little work that has been done on the relation between histamine

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and if it does not initiate an ulcer might act to prevent one healing In peptic oesophagitis duodenal ulcer and anastomotic ulcer this unopposed action of pure gastric juice may be significant

Though the procedure of continuous aspiration of nocturnal juice cannot be considered satisfactory and repeated results show considerable variation most workers agree that the mean output of acid from chronic duodenal ulcers is considerably raised to something like 3-4 times the normal the output from gastric ulcer is somewhat diminished while the stomachs of patients with carcinoma produce least of all (Levin and others 1948) As with the ordinary histamine injection the maximal output must be related to the secretory cell mass but whence comes the stimulus for this nocturnal secretion ?

In general while admitting that the relation of the vagus to the release of gastrin is far from clear we believe that the stimuli to secretion are nervous and hormonal In so far as interdigestive secretion is nervous in origin it should be inhibited by atropine and in fact a considerable degree of inhibition can be obtained either with atropine or with the newer ganglionic paralysants such as the hexamethonium salts (Riddell 1951) The fact that complete inhibition is not possible does not rule out an entirely nervous origin as the dose of atropine cannot be raised indefinitely Part of the secretion may be humoral in origin but there is little doubt that the major part is nervous If the interdigestive secretion is mainly nervous in origin whence comes this abnormal stimulus ? There is here a possible link with neurogenic and psychosomatic theories of ulcer formation Before considering this topic we may summarize dogmatically our conclusions on the relation of acid secretion to ulcer formation

(a) Ulcer only occurs in the presence of acid and pepsin active ulceration never occurs with persistent achlorhydria

(b) There is no qualitative difference in acid secretion in normals and in patients with ulcer

(c) For a given stimulus there is an increased output of secretion of acid in patients with duodenal ulcer and normal or decreased output of secretion of acid in patients with gastric ulcer

(d) Differences in outputs of acid are mainly related to differences in parietal secretory cell mass

(e) Interdigestive secretion tends to be higher in duodenal ulcer patients than in normals or in those with gastric ulcers and this interdigestive secretion is largely nervous in origin

Neurogenic and psychosomatic theories

The neurogenic theory seeks to relate events in the stomach to events in the brain or in its modern counterpart to relate altered function of the stomach to emotional states of the mind It must be emphasized that the effect of emotion on the stomach can only occur through nervous or humoral channels In any complete theory it is not sufficient to delineate in the ulcer patient a particular type of personality or emotional state it is also necessary to describe the appropriate channel or mechanism through which these changes can be effected and these changes might act on either side of our primary equation

Rokitansky a century ago first suggested that ulcer might be due to a diseased

response and the parietal secretory cell mass (Guiss and Stewart 1948) shows a significantly high correlation and is consistent with the view that output of acid is related to the number of functioning parietal cells present In practice it is not convenient to use intravenous histamine and in the case of ulcer subjects a sub cutaneous dose of histamine is commonly given The resulting acid output is a combination of factors of which the secretory cell mas plays the more important part It should be noted that measurement of the concentration of acid after stimulation with subcutaneous histamine introduces an unwanted variable the rate of diffusion of histamine from the subcutaneous depot and constant results can only be obtained by measuring the acid output which is independent of the rate of diffusion (Öbrink 1948) Measured in this way the output of acid from patients with duodenal ulcer is higher than normal whereas that from stomachs with gastric ulcer is normal or lower than normal Meyers (1948) showed that the number of parietal cells in the stomach was high in duodenal ulcer and diminished when gastric ulcer was present and if we infer as a working hypothesis that high output is a rough measure of secretory cell mass then duodenal ulcer exists in stomachs with a large secretory cell mass The experience of gastroscopists tends to confirm the association that achlorhydria and atrophic change as seen endo scopically are correlated and that increased acid output and the hypertrophic cobble stone appearance tend to be found together (Magnus and Rodgers 1938 Ricketts and others 1949) Whether ulcers only occur in those stomachs with a naturally high secretory cell mass or whether the presence of a chronic duodenal ulcer actually produces hypertrophy of the parietal cells is not known Such a self perpetuating mechanism would explain one of the vicious circles of the ulcer disease

The response to a meal is often measured by the traditional fractional test meal procedure This method leaves much to be desired It is not a standardized pro cedure it makes no allowance for dilution by saliva the emptying rate of the stomach or the regurgitation of duodenal juice nor can it hope to separate the juice into its parietal and non parietal components A single estimate of acidity attempts to measure some six variables and it need not surprise us that this ritual so assidu ously practised for over half a century has yielded such meagre results It can be of little value unless it is made a standardized procedure using a dilution indicator method as suggested by various authors Further *if food in the stomach is affecting* secretion through a gastrin histamine mechanism we should obtain much the same knowledge of secretion by using histamine direct

Interdigestive phase

Secretion may continue when the food has left the stomach and this phase of secretion called the *interdigestive phase* has attracted attention since Henning and Norpoth (1932) first measured the night secretion After the evening meal secretion normally tends to die down but in certain people notably those with chronic duodenal ulcers secretion may continue at an astonishing rate throughout the night It is not uncommon to find a case in which 1½ litres of decinormal acid is secreted in 12 hours Secretion is normally buffered by the food which provokes the response whether milk or a pork pie and the interdigestive phase of secretion when the juice remains unbuffered may be the all important and dangerous phase

abnormal autonomic discharge but these conditions do not lead to organic change such as ulcerative colitis nor does a persistent effort syndrome end in organic heart disease

On the type of investigation which claims to find a particular ulcer personality in association with ulcer it is difficult to comment Where such investigations have been uncontrolled and have depended on subjective assessments they provide no more than suggestions for further work Where they have been properly controlled the more frequent occurrence of neurotic traits has sometimes been found Unfortunately neurotic is one of the many ill defined words in psychiatric nomenclature and it is difficult to see how this important line of thought can reach any satisfactory conclusions until words like neuroticism are operatively defined and a metric approach to personality is devised and used Until then such propositions as an ulcer personality exists are either mere assertions or represent the private personal experience of the investigator Such statements may be true but they are not yet scientific facts

MUCOSAL RESISTANCE

It is clear that acid pepsin secretion *per se* cannot account for all peptic ulcer and though prolonged secretion of large amounts during the interdigestive period might account for some cases of oesophageal duodenal and anastomotic ulcer it could not by itself account for gastric ulcer in which secretion is often decreased An equally important and relatively neglected factor must lie in mucosal resistance Experimentally mucosal resistance seems to differ in different parts of the gastro intestinal tract and Price and Lee (1946) found that when various living tissues were implanted into the stomach the gastric mucosa showed the highest immunity to digestion Whether this is due to some inherent resistance of the stomach or merely to the fact of mucus protection is not clear

Mucus

One of the major protective factors in the stomach must lie in the mucus and the mucous secreting layer and this protective action was first observed by Harley Unfortunately the exact chemical nature of mucus and the stimuli to its secretion are unknown It is possible that its physical properties are of greatest importance and Hollander (1950) has also emphasized the very rapid regeneration of the surface layer of secreting cells after desquamation following prolonged irritation In direct observations on stomach mucus in their subject Tom Wolf and Wolff found that it was immediately secreted following any physical or chemical injury and that with strong hydrochloric acid it was precipitated into an insoluble and very adherent layer On an area of the mucosa in which mucous secretion was defective a typical chronic peptic ulcer was produced in four days by the continuous action of gastric juice It healed rapidly in three days with no more than a protective dressing Here then is the artificial production of an ulcer produced by gastric digestion once the mucous protective layer is absent If mucus plays a prominent part in the protection of the mucosa the existence of mucolytic enzymes assumes importance This group of enzymes was first described by Fleming (1932) who hoped to develop from it a suitable antibiotic They have been found in various secretions of the body including the stomach and duodenum and their status is

innervation of the stomach owing to a morbid condition of the vagus and to extreme acidification of the gastric juice After interest had been developed in the autonomic nervous system by Langley and other physiologists Eppinger and Hess described two types of autonomic reactors the vagotonics and the sympatheticotonics Though today these concepts are so crude as to be valueless they do at least draw attention to different states of autonomic balance and von Bergmann applied these ideas to the aetiology of peptic ulcer Later Cushing (1932) recalled attention to the association of ulcers with certain pathological states of the brain such as tumour thrombosis or brain injury It should be noted that all the ulcers so produced are acute and not chronic ulcers and various experimentalists have tried to find methods of producing peptic ulceration by stimulating certain areas of the brain particularly the hypothalamus In a certain number of cases acute lesions have been produced It has then been argued that certain mental states associated with stress might produce an abnormal autonomic discharge with for example continued secretion and that this acting on an empty stomach might produce ulceration There is some clinical evidence to support this association Most physicians have encountered striking instances of haemorrhage or perforation occurring shortly after some emotional trauma That ulcer perforations increased during the period of heavy air raids over Britain seems undoubted (Morris and Titmuss 1944) and though this finding is capable of other interpretations it is consistent with the theory of anxiety as a cause of ulcer activity and perforation

Observations on the relation of gastric function to emotional states have been made in what is now a classic study by Wolf and Wolff (1943) on their subject Tom In this subject a gastric fistula allowed direct observations of the stomach the colour of the mucosa its secretion and its motility these observations were made under different naturally occurring emotional states Wolf and Wolff noted in Tom two types of reaction (1) a depression of acid output motor activity and vascularity and (2) an acceleration of these functions The first was associated with a reaction of withdrawal from a stressful situation and the second with repressed aggression In a woman with a gastric fistula Crider and Walker (1948) made similar observations but failed to note the same relation of gastric function to emotional state that Wolf and Wolff had described in their male patient Thus though an emotional situation can profoundly alter gastric function the response of the stomach need not be the same from patient to patient That a given emotional state can produce different facial expressions in different persons is in accord with everyday experience On meeting an examiner in a *viva voce* examination there is extreme difficulty in assessing his attitude from watching his face When we know a person well we can guess his attitude fairly closely but his particular responses are individual and not universally applicable Experimental attempts of the psychologists to relate a given facial expression to an emotional state have failed If the facial expression is such an unreliable indicator of emotion will the stomach be any more accurate ?

It is tempting to apply these observations of Wolf and Wolff on the relation of gastric function and emotion to the problem of chronic ulcer and assume that if a certain stressful emotional state could be maintained chronic ulcer would result Though this may be true the argument from analogy in other parts of the body does not support it Emotional states can readily affect the colon and the condition of irritable colon and nervous diarrhoea are commonly thought of as due to

Hormonal

One of the outstanding facts of ulcer is the sex ratio of incidence and mortality and it is clear that the female is relatively immune Over which period of life does this immunity run ?

If the proportion of males to females dying from all diseases be plotted for different age groups it will be found that this sex ratio is roughly constant at about 1 2 throughout life that is 12 or 13 males die for every 10 females If now the sex ratio of ulcer deaths is plotted for various age groups it will be seen that for the age periods after puberty there is an increasing proportion of males to females dying but that before puberty though very few ulcer deaths occur the sex ratio is the same as for all causes of death After the menopause the sex ratio tends to diminish These results were interpreted by Ivy and Martin (1949) as showing either that femaleness exerts a favourable effect on ulcer mortality or that after puberty there exists exogenous factors in the environment to which the male is more exposed than the female

Sandweiss (1939 1945) has pointed out the rarity of ulcer during the course of pregnancy an event which seems to exert a highly protective action He therefore tried the effect of various extracts of pregnancy urine on experimentally produced ulcer in dogs and was able to show that such extracts can exert a definite protective effect Further investigation of this urinary extract showed that it also exerted an inhibitory action on histamine secretion Both these effects were later shown to be independent of the urinary content of the known hormones and could also be obtained by extracts of the urine from non pregnant females and males To this extract the name urogastrone has been given There is no doubt experimentally that a powerful histamine inhibitory substance occurs in normal urine which is possibly separate from the ulcer protective action Unfortunately the separation and purification of these substances has proved very difficult and judgment of their physiological status must be suspended until they have been obtained in purer form

A rather similar hormonal action on the function of the stomach has derived from a different train of thought (Ivy and others 1950) It is an old observation that fat in the intestine exerts an inhibitory effect on gastric secretion and motility Proof that this inhibitory effect was due to a humoral agent was established when inhibition was demonstrated in auto-transplanted pouches of dogs The next step was to reproduce this effect by the injection of an extract of the upper part of the small intestine this was successfully done and the extract has been named enterogastrone Enterogastrone was then given to dogs with experimental ulceration to see if any protective effect could be established A protective effect was produced which not only prevented the occurrence of ulceration so long as it was given but most strikingly produced prolonged immunity after it was discontinued This protective effect which has not yet been confirmed could not be explained purely in terms of the acid inhibitory action Though this substance has been tried in human peptic ulcer without any convincing therapeutic effect this does not detract from its great physiological interest

Both of these lines of work which seek to investigate and to isolate humoral factors affecting gastric function and which protect the muco a against ulceration

still the subject of experiment Such agents might obviously play a role in the aetiology of ulcer

Nutrition

Since malnutrition can adversely affect almost any tissue of the body it is hardly likely that the stomach would escape and there are numerous experiments in which ulceration has been produced in animals on various deficient diets The relevance of these experiments to naturally occurring ulcer in man is not clear and it seems unlikely that malnutrition plays an important part in the aetiology of ulcer in Great Britain It is however possible that it does so in such countries as India and Somervell (1948) with great experience of ulcer is emphatic on this point The only evidence that might be consistent with malnutrition as a cause of ulcer in this country lies in the mortality figures from gastric ulcer when plotted by social groups These show a definite relation of mortality to social status such as that the lowest income group has the highest mortality No such difference exists in deaths from duodenal ulcer

Blood supply

A century ago it was suggested that only a vascular factor could account for the localized lesion of peptic ulcer Could infarction of an area of the stomach mucosa occur in the presence of acid and pepsin it would readily be digested to form an ulcer Such ulcers have been produced by various methods Having noted haematemeses in cases of fracture with fat embolism in man Wangensteen (1945) tried the effect of injecting fat into rabbits with the simultaneous administration of histamine in beeswax The rabbits were unaffected by the histamine preparation alone but the combination of the two resulted in perforated ulcers in nearly all the animals These results were interpreted as due to digestion of ischaemic areas of the mucosa There seems no reason why thrombosis should not occur in end arteries of the stomach in human subjects with arteriosclerosis and this would account for the ulceration seen in elderly patients with no previous history whatever of an ulcer dyspepsia Characteristic of this type of ulceration is the sudden onset of symptoms often dated to a day and the rapid healing that follows Burger (1947) has drawn attention to the striking parallelism between the incidence and growing frequency of angina pectoris and peptic ulcer in cases seen in Leipzig between 1931 and 1941 and interprets this as showing that both diseases have a common cause

Though arteriosclerotic infarction may explain the elderly group of ulcers it can hardly explain ulcers in younger age groups free from vascular disease and for this group there has not until recently been any anatomical basis on which a vascular theory could be satisfactorily sustained Barclay and Bentley (1949) however using an injection technique of radio opaque material into the stomach vessels claim to have demonstrated the existence of an arterio venous shunt in the submucosa which when open might produce relative ischaemia of the overlying mucosa They suggested that this shunt was under the control of the sympathetic nerves If this shunt operates during life and produces localized areas of ischaemia conditions would exist for peptic ulceration The demonstration of this shunt may have given the vascular theory a fresh lease of life

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are of profound importance and may not only contribute to our knowledge of ulcer aetiology but may point the way to a new therapy

CONCLUSION

In conclusion we may say that it is most unlikely that peptic ulcer has a single universal cause From the great frequency of ulceration it is clear that a delicate balance exists in the body which needs very little disturbance to tip the scales against the patient There are likely to be multiple causes any one of which may be operating at one time or in one place the cause of ulceration in the Southern Indian peasant is not necessarily the same as that of the London stockbroker The only common cause to all ulcers is the presence of acid and pepsin present in excessive amounts in certain cases of duodenal ulcer It would seem that in the past undue emphasis has been placed on the production of acid and pepsin and too *little attention has been focused on the protective factors which have been much less* studied and far less understood

Perhaps in searching for the cause of ulcer we should emphasize this by asking *our question the other way Why do people not get ulcers ?*

REFERENCES

Adam H M Card W I Riddell M J Roberts M and Strong J A (1951) In press
Barclay A E and Bentley F H (1949) *Brit J Radiol* 22 62
Burger M (1947) *Altern und Krankheit* p 268 Leipzig Georg Thieme
Crider R J and Walker S M (1948) *Arch Surg* 57 1
Cushing H (1932) *Surg Gynec Obstet* 55 1
Fisher R B and Hunt J N (1950) *J Physiol* 111 138
Fleming A (1932) *Proc R Soc Med* 26 71
Guiss L W and Stewart F W (1948) *Arch Surg* 57 618
Henning N and Norpoth L (1932) *Arch VerdauKr* 53 64
Hollander F (1950) *Post Graduate Gastro Enterology* ed by H L Bockus London Saunders
Ihre B J E (1939) *Human Gastric Secretion* London Oxford University Press
Ivy A C and Martin C G (1949) *Gastroenterology* 13 215
— Grossman M I and Bachrach W H (1950) *Peptic Ulcer* p 439 London Churchill
Levin E Kirsner J B Palmer W L and Butler C (1948) *Arch Surg* 56 345
Magnus H A and Rodgers H W (1938) St Bart s Hosp Rep 71 129
Meyers W C (1948) *Gastroenterology* 10 923
Morris J N and Titmuss R M (1944) *Lancet* 1 395
Öbrink K J (1948) *Acta physiol scand* 15 *Suppl No* 51
Price P B and Lee T F (1946) *Surg Gynec Obstet* 83 61
Ricketts W E Palmer W L Kirsner J B and Hamann A (1949) *Gastroenterology* 11 789
— Kirsner J B and Palmer W L (1949) *Amer J med Sci* 217 542
Riddell M J (1951) In press
Sandweiss D J Saltzstein H C and Farbman A A (1939) *Amer J digest Dis* 6 6
— *(1945) Gastroenterology* 5 404
Somervell T H (1948) *The Surgery of the Stomach and Duodenum* London Arnold
Wangensteen O H (1945) *Canad med Ass J* 53 309
Wolf S and Wolff H G (1943) *Human Gastric Function* London Oxford University Press

SECTION III

TREATMENT AND PROGNOSIS

THOMAS HUNT

DOCTORS are often slow to learn from patients but in the treatment of peptic ulcer experience has gradually convinced them that patients who broke the rules some times did better than those who stuck too rigidly to them Regimes of ladder diets meticulous food restrictions and exacting rules were not in fact producing good results Reports of 50–100 per cent of relapses within 3–5 years amongst even the most careful patients were not infrequent In addition attempts at neutralization of gastric acidity with various antacids were found to be equally unsuccessful and a tendency to abandon alkali treatment altogether began to develop In the place of these two lines of treatment by strict dieting and alkalis a newer school of thought emphasized the importance of sedation and began to regard pheno barbitone as the only drug ever called for in the treatment of peptic ulcer [1]

It is certain that the present view of the aetiology of peptic ulcer offers a more rational line of treatment than the older one where the whole problem was thought to lie in controlling gastric acidity It is now realized that whilst gastric ulcer may be a disease due in part to dietetic and environmental factors such as poor nutrition bad dentition infection and the like duodenal ulcer is more a constitutional disorder associated largely with psychological factors such as anxiety frustration and suppressed resentment In other words a disease more of emotional origin related to conditions of strain and worry than a disease of dietary deficiencies or excesses

REGIME AND DIET

In consequence of this conception of aetiology the broad principle of treatment has come to stress more than formerly relief from worry and a regular routine and less the precise items of food that are allowed or forbidden Medical treatment thus demands not only a period from 6 to 8 weeks rest but a determined effort on the part of the physician to adjust the patient s life afterwards as regards his responsibilities hours of work times of meals holidays and general attitude to work and leisure Combined with this attempt some sedative is often useful and though many have been tried phenobarbitone still remains the most popular and generally satisfactory one It is at times rather depressing and should not be used to the extent of causing actual drowsiness Carbromal 5 grains one or twice a day is sometimes a successful alternative and Douthwaite (1947) has advocated cannabis indica in large doses partly on account of the euphoria it produces It is usually possible to lessen the many necessary and unnecessary activities in which duodenal patients nearly always indulge but their disposition to worry over the least thing often remains unaltered and is probably the greatest single cause of

the high frequency of relapse Psychotherapy in the form of individual interviews relaxation exercises and occupational therapy has indeed been employed with success by some workers (Selesnich 1950)

Diet

Whilst emphasizing this need for moderation in work play and emotional reactions to trivial events it is important at the same time to give the patient as free and as full a dietary regime as he can tolerate

Monotonous and unappetizing meals are unlikely to prevent recurrences provided meals are taken regularly and at frequent intervals it is surprising what unrestricted foods may safely be allowed Most of the old lists of forbidden foods are in fact unnecessary and when it is remembered that milk itself has only a transient and uncertain action in reducing gastric acidity the rationale for avoiding many of them falls to the ground If the patient finds he is able to take foods without pain or discomfort it is certainly wrong to forbid them on the simple grounds that they may stimulate gastric acid secretion If on the other hand they are foods which cause pyloric spasm and gastric overaction tending to remain long in the stomach it is probable that they will cause discomfort delay healing and should be avoided Such are tough meat poorly masticated hard foods such as nuts thick marmalade peel and hot fatty foods The latter are particularly liable to cause gastric hypermotility in contrast to cold fats such as cream and butter which have the opposite effect of inhibiting both motility and acid secretion The longer a fat is heated for example by frying the more the saponified fats disappear and the more unsaponified fats which stimulate gastric motility remain

Alcohol must be restricted and should be completely forbidden during the initial healing stages of treatment It acts as a stimulant to gastric secretion possibly in part by indirectly releasing histamine and if allowed after the period of active treatment should be given dilute and with food Tea and coffee are also gastric stimulants a large cup of strong tea containing as much as 2 grains of the alkaloid caffeine Coffee contains some 15 per cent of aromatic oily matter in addition and is for this reason more irritant than tea Its effect on gastric secretion in ulcer patients seems to be greater than in others and experimental evidence suggests that it is able to increase the secretogogue effect of histamine in some synergistic way

The experimental evidence however of a given article of diet on gastric secretion alone is no good criterion of its effect on clinical symptoms and ulcer healing As mentioned above the fact that milk and milk mixtures have little significant effect in reducing gastric acidity in spite of their proved value in ulcer treatment is evidence of this (Kirsner Levin and Palmer 1948) Whatever may be the exact antacid qualities of an ulcer diet no relaxation must be allowed as regards times of meals and intervals between them which should never be longer than 3 hours During the initial period of rest feeds should be given every 1 or 2 hours but the old regime of gradual increases in amounts is unnecessary Hunger should be avoided It is vitally important to achieve if possible complete healing at the first attempt and to allow the full period of 6–8 weeks rest as partial healing makes success at the next attempt much more difficult

Smoking

Smoking still remains a subject of argument but the majority of those who have studied its effect in recent years in cases of peptic ulcer have concluded that whilst not acting as a causative agent it nevertheless increases the liability to relapse Thus Batterman and Ehrenfeld (1949) found that the relapse incidence in a small number of 109 ulcer patients whom they studied was approximately 3 times as great amongst smokers as amongst non smokers and they consider that the nicotine absorbed in smoking definitely lessens the response to medical treatment Gainsborough and Slater (1946) also noted that the only factor they could detect significantly associated with relapse rate in 93 ulcer patients was smoking—even including indications of anxiety tendencies Jamieson Illingworth and Scott (1946) however in Glasgow concluded from their study of 473 ulcer patients who had all suffered from acute perforation that changes in tobacco consumption had not influenced the severity of their symptoms they suggested that cigarette smokers tend to have severe symptoms because they are in the main young subjects whereas pipe smokers who are more often older people tend to have milder symptoms

Whatever may be the whole truth of the relationship of ulcer to tobacco there is in my opinion one real danger in smoking namely that the smoker may readily light a cigarette when he is hungry and a meal is difficult to get and so be more likely to miss this meal than the non smoker who has no such substitute for his food!

ANTACIDS

The newer antacids that have been introduced during recent years have the great merit that they carry no risks of causing alkalosis In the main they belong to the magnesium trisilicate group the aluminium hydroxide group or to a mixture of these two together The former tend to cause diarrhoea and often troublesome borborygmi and discomfort the latter are often constipating Their action in neutralizing gastric acid is not very high in comparison to such alkalis as magnesium oxide but they inactivate pepsin and act as adsorbents and astringents whilst not themselves being absorbed into the circulation Magnesium trisilicate for example whilst theoretically a good antacid in its safety and relatively prolonged action is often less effective in relieving symptoms than bicarbonate of soda which causes a considerable secondary rise in acid secretion and only an extremely transient neutralizing effect

Batterman and Ehrenfeld (1947) who made a study of most of the known antacids in respect to their effectiveness in relieving symptoms and as acid neutralizers concluded that the combination of an aluminium hydroxide and a magnesium trisilicate preparation—such as Gelusil—was the most efficient of the preparations they tested Recently Mutch (1949) has described the effect of activated phosphates which are complexes of hydrated silica and tribasic calcium or magnesium phosphate and has shown that these substances give good results clinically and act by adsorption as well as by neutralization

In my opinion one special value of such tablets as these is that they may be carried in the pocket are not unpleasant to chew and can and should be taken the moment any pain occurs whatever time of day or night it may be almost any

amount needed to relieve the symptoms can safely be taken There is indeed little rationale for the routine use of antacids at regular fixed intervals but good clinical reasons for their use at the first moment pain begins before it has had time to become established by which time it is far more difficult to relieve

Newer antacids

Much experimental work has been carried out since the war on other substances which depress or inhibit gastric secretion or motility partly at least with the object of applying such substances to the treatment of peptic ulcer Tetraethyl ammonium bromide is one such substance which though acting as a powerful depressant of gastric function has too short an action and too unpleasant side effects for example upon blood pressure to make it as yet a useful therapeutic agent in peptic ulcer Dibutoline is another product which acts as a parasympathetic drug and given subcutaneously is able temporarily, to suppress gastric secretion completely and lessen gastro intestinal motility Lorber (1950) has compared the effects of this drug with those of atropine in a number of cases of duodenal ulcer and found it equally effective and with fewer side effects such as dryness of the mouth Hexamethonium iodide is a third preparation which appears to act by impeding nerve impulse transmission and has a marked action on gastric secretion and motility Kay and Smith (1950) in Glasgow have shown that 100 milligrams of this substance given subcutaneously may produce achlorhydria for as long as 3 hours and cause cessation or diminution of gastric contractions and tone It acts thus in a comparable way to vagotomy and in the 12 duodenal ulcer patients studied by Kay and Smith seemed to cause no untoward effects

Various synthetic resins have also been tried as neutralizing agents and have been shown to reduce acidity and inactivate the pepsin of gastric juice Several investigators have described the use of such anion exchange resins which they have found to relieve pain and epigastric discomfort when given in adequate dosage According to Wirts Sullivan and Hemmesley (1950) their clinical value in the treatment of peptic ulcer is at least as great as that of aluminium hydroxide whilst their side effects are slight and present no practical bar to their use The dose given was one gram I have no personal experience of their use but they would not seem to offer any great advantage over other antacids

Milk hydrolysates and various mucin preparations have been employed as antacids during recent years but so far have not shown any great advantages over simple milk feeds in the relief of pain Their action in reducing acidity is variable but their value clinically does not run parallel with this in some hands such hydrolysed protein mixtures have given good results in ulcer treatment but these are probably not superior to those following the more usual dietary regimes Mucin has theoretically valuable protective properties against hydrochloric acid but hitherto tests using hogs mucin by mouth in ulcer treatment have not been very widely followed up

Enterogastrone

Kosaka and Lim (1930) and Ivy and his co worker (1937) showed many years ago that extracts of upper intestinal mucosa contain a substance which is capable experimentally of inhibiting gastric secretion and motility under certain conditions

Similar effects can also be produced by intravenous injection of certain extracts from urine either human or animal whether pregnant or not. Various such extracts have been employed in the treatment of ulcer and the general terms enterogastrone and urogastrone are used to designate them. They probably include a number of different substances; numerous reports are available on their use both experimentally and in ulcer patients (Ivy and others 1949). A protein free substance prepared from gastrin and intestinal tissue called Robuden has for example been used extensively in Switzerland both orally and by intramuscular injection. The literature on these substances is contradictory (*see* Stolte 1950) and for the most part the clinical results do not bear critical analysis. It seems certain that more than one active substance is concerned and that some definite effects are produced on gastric activity and on ulcer healing. Nevertheless the results on the whole are not encouraging and Sandweiss and others (1948) for example found that enterogastrone treatment in their cases gave less satisfactory results than the usual diet alkali regime.

Milk drip

The use of a continuous milk drip has certain advantages both theoretically and in practice. It is however employed by most physicians only in cases not responding to the customary treatment by rest and diet. In theory this method should maintain continuous neutralization of the gastric juice both by day and also by night when acid secretion in duodenal ulcer patients is usually abnormally high. If 5–6 pints of milk in 24 hours are given neutralization may perhaps be achieved but it must be realized that ulcer healing can also take place satisfactorily even when acidity is reduced only moderately and not by any means continuously. If the tube is passed through the nose and two or three meals a day are given in addition to the milk drip patients tolerate the treatment fairly well though older patients in whom it is often most needed are apt to find it difficult and irksome in some the nasal route is liable to set up irritation. Various minor difficulties are often found in using this treatment but it is certainly effective in the rapid relief of pain and many reports (Winkelstein and others 1942 Garlik 1949) have given very favourable accounts of its results. As in all forms of treatment for peptic ulcer the interest and enthusiasm of those who give the treatment and the emotional stimulus of having a continuous drip running must be taken into account in assessing its mode of action. Details of its use are given in most up to date text books of medicine.

Radiation therapy of ulcer

Irradiation of the stomach produces change in the stomach mucosa ranging from redness oedema and bleeding to actual atrophy of the lining. In consequence of this irradiation gastritis gastric acidity is reduced and it is readily possible by suitable dosage to produce a fairly long lasting achlorhydria. Ricketts and others (1949) have reported results in over 800 cases of peptic ulcer treated in this way but stress the difficulties of finding the correct dosage and the marked variations in response in different individuals. The method is not without danger and has not been generally adopted but is certainly capable of producing satisfactory ulcer healing even though it has little permanent effect in preventing later recurrence.



(a)



(b)

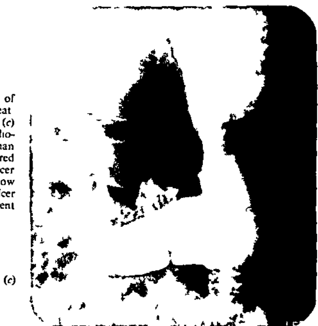


Fig 167—Rate of healing of peptic ulcer (a) Start of treatment (b) after 16 days (c) after 30 days Serial radiographs (barium meal) in a man of 70 years who had suffered from symptoms of gastric ulcer for 30 years Photographs show disappearance of the ulcer crater under routine treatment by rest and diet

Protein shock

Widespread claims made for the success of Histidine injections as a specific treatment for peptic ulcers have long since been disproved Nevertheless some response to large (5 millilitres) injections of almost any sterile fluid given intra muscularly for example saline glucose amino acid solutions may commonly be observed Such improvement in healing does not appear to be wholly psychological and may be due in part to a mild protein shock effect from the small haematoma formed in the muscle with resulting slow blood absorption It is certainly in my experience interesting to note how in a few slow healing or intractable cases a course of 6 or 8 daily such injections in addition to the normal routine medical measures sometimes hastens the response to treatment

PROGNOSIS

The great majority of ulcers treated medically will heal within 6 weeks even when conditions are not ideal Many studies of healing times have established a period of 20–40 days as an average with extremes between 15 and 200 days (Cummings and others 1946 Wirts and others 1950) Unexpectedly however this healing time is not strictly related to either the size of the ulcer the length of the previous history or the age of the patient In general a small and recent ulcer in a young patient would be expected to heal more quickly than a large ulcer in an older man but such is by no means always the case Fig 167 for example shows the healing of a large ulcer in a man of 70 who had had symptoms for over 30 years under a simple regime of rest and regular feeding In spite however of the most careful

treatment a proportion of apparently uncomplicated cases will fail to heal satisfactorily This proportion seems to remain at about 15 per cent in almost all reported series and corresponds closely also to my own experience Of this group a few are probably due merely to the chronic inflammatory changes around the ulcer producing so much thickening that a vascular block is produced as has been demonstrated beautifully by Key (1950) using the method of micro angiography Others have in fact some associated disease or unrecognized complication such as cholecystitis pancreatitis or chronic perforation with much thickening and ischaemia of the ulcer base but the remainder must be grouped as intractable without any certain reason being found In some there is a strong family history of ulcer in others an intense anxiety state with a temperament incapable of relaxation In a few it seems as if some inhibitory factor is preventing healing the nature of which is unknown It is in such cases that special treatments such as a milk drip should be tried but unfortunately it is often just these bad medical cases which also make bad surgical cases and their prognosis as regards lasting good health is far from good Any patient who fails to show a response to treatment within 2–3 weeks must be most carefully reviewed at once to exclude complications (for example adhesions) or associated disease (for example cholecystis) and it is often at this stage that the decision whether to persevere with medical treatment or advise surgery at once has to be taken this however is discussed in more detail on page 397

After the healing period is over the main problem—that of recurrence—arises As previously mentioned more than half the cases treated medically relapse within 3 years and about three quarters within 5 years The longer the duration of symptoms before treatment and the less thorough such treatment the higher is the probability of early relapse Althausen (1949) summarizing some 10 other series and his own cases a total of over 3 000 finds a relapse rate of 50 to 90 per cent within 5 years whilst Marten and Lewis (1949) and others report figures at least as high Some of the factors causing this high relapse rate can be assessed others are unknown Occupational stresses such as interrupted meals alternating day and night duty prolonged mental strain and fatigue recurrent respiratory infections and chills are some smoking unsuitable diets and emotional disturbances in home life are others Hussar (1948) in reporting a recurrence rate of 94 per cent in 305 ex service duodenal ulcer patients over an average period of 3 years mentions another possible factor in these cases namely the disability compensation or secondary gain involved Failure to start treatment at the earliest moment after any return of symptoms is an important additional point Nevertheless in spite of such possible causes many recurrences take place under good conditions without any reason that can be discovered and frequently patients complain that symptoms have returned even though they have meticulously followed their dietary rules At least 30 per cent of perforations and many cases of haematemesis for example occur without any apparent provocation whatever and with no dietary excess emotional shock or other obvious cause It is thus unfortunately true that many careful patients do not deserve their relapse whilst others who relax their regime and might expect recurrence do not always have one In spite of this definite clinical observation it is still generally agreed that the risk of ever discarding a sensible post ulcer regime is too great to justify giving such

advice and most authorities as regards treatment accept the life sentence of once an ulcer always an ulcer

In view of these poor long term results of medical treatment and the difficulty of guaranteeing any freedom from recurrence it might be argued that the earlier radical surgery is undertaken the sooner is a patient likely to be free from irksome restrictions and safe from further attacks The indication therefore for surgical treatment would on this view merely be the diagnosis of a chronic ulcer The main reasons why this is not so are first that no surgical procedure yet devised provides a certain guarantee against future trouble and secondly that the mortality risks of adequate surgical treatment in Great Britain as a whole are certainly not less than 3 to 4 per cent whilst post operative morbidity in some series is as high as 50 per cent (Milstein 1949) Allowing however for these risks skilled surgical treatment by gastrectomy offers a prospect of between 80 and 95 per cent cure in the sense that patients remain virtually free of symptoms for good and are able to eat normal food and live normal lives They are moreover if they develop no post operative complications and do not die from the operation almost free of any danger of haemorrhage perforation or pyloric stenosis one of which is ultimately likely to develop in about one quarter of all cases of ulcer treated medically Furthermore in the case of gastric ulcer the danger of a malignant ulcer being mistaken for a benign one is so considerable that the risks of surgery are more than counterbalanced So real indeed is this risk of a supposed pyloric ulcer being in fact a carcinoma that immediate gastrectomy of all ulcers in this situation is perhaps the treatment of choice as it certainly is for any supposed peptic ulcer on the greater curvature Nevertheless for elderly patients with anything but the best surgeon and very skilled pre and post operative care the mortality of this operation is in general not less than 8 to 10 per cent even though it is as low as 1 to 2 per cent under ideal conditions Unoperated upon the mortality rate of peptic ulcer is at the present time a little lower than the mortality rate of operation and it must not be forgotten that many individuals live long and active lives with clear evidence after death of healed but untreated ulcers moreover ulcer recurrences are by no means always incapacitating Patients should be told these broad probabilities when the question of surgical treatment is first proposed and they should weigh up themselves the risks of recurrent disability and absence from work with some life long restrictions on medical treatment against the higher risk of dying but a smaller risk of a worried future on surgical treatment Though these considerations apply to many cases there always remains a number of clear-cut and definite indications for surgery which require that the physician insist rather than merely advise the patient to undergo operation These indications are briefly as follows

(1) Pyloric obstruction not responding fully to a short course of medical treatment treatment

(2) Perforation acute and chronic

(3) Severe haemorrhage in a known chronic ulcer case *if operation can be performed at once under good hospital conditions*

(4) Persistent pain after proper medical treatment especially is spreading severely to the back (probable adherent ulcer or chronic perforation)

(5) A history of frequent recurrences over 10 years or longer even in young patients and even if there has been no thorough m dical treatment undertaken

(6) A history of one or more recurrences in a patient over 45 years after thorough medical treatment especially if it is impossible to adjust his work and diet to a suitable regime

In all these problems of advising between medical and surgical treatment much must depend upon the skill and experience of the surgeon available the type of operation to be performed and the temperament age and degree of arteriosclerosis of the patient

REFERENCES

Althausen T L (1949) *Ann intern Med* 30 544
Batterman R C and Ehrenfeld I (1947) *Gastroenterology* 9 141
— — (1949) *Ibid* 12 575
Cummings G M Crossman M and Ivy A C (1946) *Ibid* 7 20
Douthwaite A H (1947) *Brit med J* 2 43
Gainsborough H and Slater E (1946) *Ibid* 2 252
Garlick H W (1949) *Med J Aust* 2 453
Hussar A E (1948) *Gastroenterology* 11 183
Ivy A L and Gray J S (1937) *Cold Spr Harb Symp quart Biol* 5 405
Ivy A C Littman A and Grossman M (1949) *Gastroenterology* 12 715
Jamieson R A Illingworth C F W and Scott L D W (1946) *Brit med J* 2 288
Kay A W and Smith A N (1950) *Ibid* 1 460
Key J A (1950) *Ibid* 2 1464
Kirsner J B Levin E and Palmer W I (1948) *Proc Soc exp Biol N Y* 69 108
Kosaka J and Lim R K (1930) *Ibid N Y* 27 890
Lorber S H (1950) *Post Grad Gastroenterology* p 34 Philadelphia and London Saunders
MacDonald I R and Smith A H (1949) *Brit med J* 2 620
Marten L and Lewis N (1949) *Lancet* 1 1115
Milstein B B (1949) *Ibid* 1 514
Mutch N (1949) *Ibid* 1 852
Ricketts W E Palmer W L and Hamman A (1949) *Gastroenterology* 2 789
Sandweiss J J Sugarman M H and Lockwood B (1948) *J Amer med Ass* 138 552
Selesnich S (1950) *Gastroenterology* 14 364
Stolte J B (1950) *Lancet* 2 858
Winkelstein A (1942) *J Amer med Ass* 120 743
— Cornell A and Hollander F (1942) *Ibid* 120 743
Wirts C W Sullivan B N and Hemmesley W (1950) *Gastroenterology* 15 1

SECTION IV

ELECTIVE SURGERY

NORMAN C TANNER

IN THE treatment of some of the complications of peptic ulcer for example perforation or severe stenosis *the clinician is confronted with a considerable risk of* death or severe incapacity for his patient unless surgical measures are undertaken In such cases the decision to operate is usually not difficult but it is a very different problem when dealing with elective surgery in the absence of acute complications In such circumstances one has to balance the discomfort incapacitation and risks of the disease against those of the operation It is important to assess its prospect of curing the lesion the possibility of recurrent ulceration or of post operative gastro intestinal or other disturbances Operative morbidities and mortalities have diminished of late years and varying success has attended the different operations that have come into use from time to time so that the problem is not static but is a changing one Needless to say any medical therapy which would improve or diminish the relapse rate of peptic ulceration would diminish the need for surgery but up to the present no very effective remedy has been discovered which will markedly influence the natural history of the ulcer (Martin and Lewis 1949)

Selection for surgery

No hard and fast indications for surgery can be laid down each case must be considered not only from the point of view of the anatomical diagnosis but also age sex occupation social circumstances and psychological outlook must be taken into consideration

Diagnosis

Modern means of investigation make an accurate diagnosis possible in nearly all the cases Surgical success will depend upon two requisites first that the symptoms were in fact due to an ulcer and secondly that the ulcer was cured by the surgical intervention

These sound straightforward criteria but the first holds two possible fallacies even if the anatomical diagnosis is correct The patient may have an ulcer scar or relatively quiescent ulcer although a coincident gastritis cholecystitis functional or nervous dyspepsia may be the true cause of the symptoms Operative intervention for the ulcer will fail to cure such cases therefore one must be wary of the patient with a quiescent ulcer who exhibits many or bizarre symptoms particularly if the usual ulcer remedies such as rest and alkalis fail to afford symptomatic relief

The second fallacy to bear in mind is rarer but is a reality The patient has had an ulcer for many years and has learnt to live with his ulcer —leading a restricted

(5) A history of frequent recurrences over 10 years or longer even in young patients and even if there has been no thorough medical treatment undertaken
(6) A history of one or more recurrences in a patient over 45 years after thorough medical treatment especially if it is impossible to adjust his work and diet to a suitable regime

In all these problems of advising between medical and surgical treatment much must depend upon the skill and experience of the surgeon available the type of operation to be performed and the temperament age and degree of arteriosclerosis of the patient

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Althausen T L (1949) *Ann intern Med* 30 544
Batterman R C and Ehrenfeld I (1947) *Gastroenterology* 9 141
— — (1949) *Ibid* 12 575
Cummings G M Crossman M and Ivy A C (1946) *Ibid* 7 20
Douthwaite A H (1947) *Brit med J* 2 43
Gainsborough H and Slater E (1946) *Ibid* 2 252
Garlick H W (1949) *Med J Aust* 2 453
Hussar A E (1948) *Gastroenterology* 11 183
Ivy A L and Gray J S (1937) *Cold Spr Harb Symp quart Biol* 5 405
Ivy A C Littman A and Grossman M (1949) *Gastroenterology* 12 735
Jamieson R A Illingworth C F W and Scott L D W (1946) *Brit med J* 2 288
Kay A W and Smith A N (1950) *Ibid* 1 460
Key J A (1950) *Ibid* 2 1464
Kirsner I B Levin E and Palmer W I (1948) *Proc Soc exp Biol N Y* 69 108
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Lorber S H (1950) *Post Grad Gastroenterology* p 34 Philadelphia and London Saunders
MacDonald I R and Smith A H (1949) *Brit med J* 2 620
Marten L and Lewis N (1949) *Lancet* 1 1115
Milstein B B (1949) *Ibid* 1 514
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Ricketts W E Palmer W L and Hamman A (1949) *Gastroenterology* 2 789
Sandweiss J J Sugarman M H and Lockwood B (1948) *J Amer med Ass* 138 552
Selesnich S (1950) *Gastroenterology* 14 364
Stolte J B (1950) *Lancet* 2 858
Winkelstein A (1942) *J Amer med Ass* 120 743
— Cornell A and Hollander F (1942) *Ibid* 120 743
Wirts C W Sullivan B N and Hemmesley W (1950) *Gastroenterology* 15 1

anaemias and this tendency is a little more marked in females Women are more often able to control their ulcer relapses better than men possibly because of their more sheltered lives and the greater control they have over the times and frequency of their meals and rest

Social conditions and occupation—In some occupations it is possible to follow a post ulcer regime and take time off from work as soon as a relapse commences Some patients find the regime no great hindrance and are not particularly keen for surgery and such sufferers will not be grateful for surgical aid The majority of occupations make an ulcer regime irksome or even impossible to follow and some workers are confronted with the alternatives of abandoning their regime or their occupation For such cases surgery is indicated Surgery can in most cases offer the patient the prospect of following a normal dietetic regime but normal does not mean that the highly strung person can smoke instead of taking his meals or that the barman or drayman can take large quantities of alcohol instead of eating even though the more fortunate may remain unharmed by such indiscretions

In these days when the majority of the population are insured against sickness and many suffer no financial loss from sick leave adequate courses of medical treatment are open not only to those with abundant means

There is a tendency for the sedentary or office worker with an ulcer to think that a change to open air work will help him and the manual worker often desires to change to sedentary work These changes are usually a waste of time and may involve financial loss and surgery should not be deferred for such trials One should weed out those patients who are exaggerating their mild ulcer symptoms with the object of achieving a change of occupation

Indications for surgery

Bearing in mind the preceding observations there are certain facts concerning the ulcer which may indicate that surgery is advisable There are few peptic ulcers which will not heal soundly if treated medically when the patient first consults the physician If the ulcer would remain healed there would be practically no place for elective surgery but it is a typical feature of peptic ulceration that the lesion is prone to periodic relapse therefore the prevention of relapse is the chief indication for surgery Thus it is the history of the case rather than the precise state of activity of the ulcer which provides most of the information required to make a decision as to the correct line of treatment

Elective surgery is practically never required for acute or subacute ulcer and the problem concerns only chronic ulcers of a minimum of three months duration

History—As indicated a history of repeated relapse despite a medical regime and previous medical healing is the prime indication The length of history and the frequency of relapses which indicate a need for surgery will vary according to the particular features of the case and according to the site of the ulcer It is usual to treat duodenal ulcers medically on two or more occasions before advising surgery and to operate but rarely unless the patient has had the ulcer for 2–3 years Too early surgery performed before the patient has experienced much discomfort may lead to an ungrateful patient particularly if he should suffer from

life but able to get along fairly happily Ulcer disease is common and will not give the patient any immunity to other diseases The ulcer patient who develops for example a carcinoma in lung kidney or other organ will with the growth of the tumour feel out of sorts—a vague feeling of ill health with at first no very notable added specific symptoms What is more likely then than that he should attribute his increasing ill health to his dyspepsia? Even if he does not the doctor may obtain a history of prolonged dyspepsia and increasing ill health and may tend to blame the lesion he discovers in the stomach for all the symptoms and recommend surgical treatment The moral here is to refrain from operating until a careful general overhaul has been made paying special attention to complaints of vague ill health or weight loss particularly in patients past 40 years of age

Age—In the young the ulcerative lesion may heal with rapidity but unfortunately is very prone to relapse In the teens the necessity to return to work is rarely pressing and so medical management should be used over a prolonged period to ensure complete ulcer healing If relapses are frequent or gross deformities appear then surgery may be necessary In middle life family responsibilities make courses of medical treatment irksome and sometimes precipitate financial crises At this time the patients tend to ask for surgery and indeed provided that medicine has been given an adequate trial surgery is often advisable However surgery should not be used merely as a time saver for most operations for ulcer will involve as much loss of time as would two good courses of medical treatment In the aged one must pay particular care to exclude severe associated disease which will prevent a successful outcome of operation When approaching retiring age some patients prefer to retire early believing that they can then devote more time to curing their ulcer by diet and rest In relatively mild cases this may work out well but in severe or complicated cases particularly of gastric ulcer their hopes may be turned to disappointment

In the aged the fear that a gastric or oesophageal lesion may in fact be carcinomatous must be particularly borne in mind and unless proof of healing and persistence of healing can be obtained surgery is indicated to exclude this possibility Whether surgery is justifiable solely to prevent the development of carcinomatous change in the ulcer is more debatable In most cases a decision can be made without the necessity of invoking this argument though it is a valid one

There is a tendency for the gastric acidity to diminish with advancing years and thus there is something to be said in favour of persisting with medical treatment in cases of duodenal ulcer later in life However this decline in acidity cannot be relied upon to occur in any individual case even though on the average there is this tendency I have even known duodenal ulcer to develop for the first time in patients in the ninth and tenth decades Therefore this hope of spontaneous reduction of acidity should not deter one from operating in a case which is otherwise suitable for surgery

The mortality from operative procedures increases after the age of 50 and operations for uncomplicated ulcer will be infrequent after the age of 65 years On the other hand the mortality from the complications of peptic ulcer particularly that from haemorrhage or perforation also increases after the age of 50 years

Sex—Operations which result in reduced gastric acidity and increased rate of gastric emptying tend to produce a certain percentage of cases of iron deficiency

anaemias and this tendency is a little more marked in females Women are more often able to control their ulcer relapses better than men possibly because of their more sheltered lives and the greater control they have over the times and frequency of their meals and rest

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post operative post cibal symptoms On the other hand the *prognosis as to permanent* relief from medical treatment of gastric ulcer is worse its complications are more lethal and the risk of neoplastic degeneration is to be considered and so many would advocate surgery if relapse occurs after one previous efficient course of medical treatment Anastomotic ulceration rarely runs a satisfactory course under medical management because of its tendency to frequent relapse often with severe complications Surgery is to be preferred except for the type of stomal ulceration which gives trouble at very infrequent intervals perhaps arising many years after operation and which is really a subacute or acute form of ulcer

If there is a history of severe complications accompanying the present or previous relapse then other factors being favourable surgical management is the safer These complications are haemorrhage massive or prolonged minor bleeding acute perforation of the ulcer perigastric or periduodenal abscess or other peritoneal abscess associated with the ulcer local peritonitis without evidence of frank perforation obstruction due to scar contraction of duodenal gastric oesophageal or stomal ulcer and gastro colic fistula

Features of the ulcer—Certain features of the ulcer indicate a desirability for surgery The wider and deeper an ulcer particularly if of very long standing and with a rigid fibrotic base the slower it will be in healing and the less likely to heal completely Generally speaking the greater the size of an ulcer the greater the risk of acute or chronic perforation or erosion of a large vessel with resultant haemorrhage It is far more dangerous to suffer an acute perforation or massive haemorrhage than it is to have a definitive operation for ulcer Occasionally at times of stress a large ulcer may appear within a few months and such ulcers may *particularly* in the young heal rapidly once medical treatment is instituted If the provocative stimulus can be removed it is worth while in such cases to try *the effect of following* a post ulcer regime rather than proceeding at once to surgery merely because *the ulcer is large in size*

When extensive ulcers heal or perhaps even more often when a small or *moderate sized ulcer repeatedly breaks down and heals over* the course of years great losses of tissue resulting in severe deformities may ensue In the oesophagus *shortening and stenosis* occur in the stomach hour glass or bizarre deformities The duodenum shortens and narrows with the production of stenosis and perhaps pre stenotic diverticula Stomal ulcers following gastro jejunal anastomosis may become stenosed with resultant dilatation of the afferent jejunal loop and perhaps gastric retention from efferent loop narrowing If the deformity is extreme surgery may become imperative as a result of obstruction to the passage of food Even if there is no such mechanical effect the fact that there is extensive scarring and deformity means that there is a lack of mobility and a thin and *often fragile* epithelium which will not stand up well to the ordinary trauma of the passage of food and peptic juice and *possibly the scarred areas are lacking in anti peptic* resistance This extensive scarring indicating as it does that hopes of prolonged remission from ulceration are *unlikely to be fulfilled* implies that surgical treatment is required

Failure of an ulcer to heal under medical treatment is an indication for surgery particularly if persistence of ulceration is confirmed radiologically or gastroscopically Persistence of symptoms despite bed rest in a patient with doubtful

or minimal ulceration should make the clinician reconsider whether the symptoms are all due to the ulcer It is unusual for ulcer symptoms to fail to respond to bed rest and medical treatment unless the ulcer is penetrating or otherwise com plicated

Certain features of the ulcer may give rise to a suspicion that it is in reality an ulcer cancer or that it is particularly prone to undergo malignant degeneration Such features are the association of a chronic gastric ulcer with achlorhydria the presence of an ulcer near or on the greater curvature of the stomach or in the pre pyloric region rigidity of the stomach adjacent to the crater the appearances of ulceration in a thickened area of stomach irregularity of the crater base or edge In some such cases innocence can be proved with little or no doubt best of all by demonstrating healing but otherwise these features should make the physician debate the advisability of extirpation of the ulcer

SURGICAL PROCEDURES IN THE TREATMENT OF CHRONIC PEPTIC ULCER

In the earlier days when the nature of peptic ulcer was less well understood operations for local extirpation of the ulcer were practised These included such procedures as diathermy excision wedge resection local excision and sleeve resection (Fig 168) The recurrent ulcer rate in the scar of resection was little less than that appearing in an ulcer scar following a good course of medical treatment Next by passing operations came into vogue particularly gastro jejunostomy for duodenal ulcer and later gastro duodenostomy and pyloroplasty (Fig 169) These were found to have an excellent effect on the duodenal ulcer particularly gastro jejunostomy but there was a high and increasing incidence of ulceration at the stoma mainly on the jejunal side With increasing awareness of the role of the gastric secretions particularly of acid in the production of ulcer attempts were made to lower the gastric acidity by surgical means The chief of these methods if one excludes methods of diverting the duodenal contents into the stomach by means of short circuits was by cholecyst gastrostomy partial gastrectomy ligation of the gastric vessels and vagotomy (Fig 170) The first is insufficient and the third does not appear to be very effective in most surgeons hands Gastrectomy has the advantage not only of reducing the gastric acidity but of removing or perhaps short circuiting the ulcerative lession Vagotomy remains and must be for another 5-10 years under trial

At present the choice of definitive operations for peptic ulcer lies almost com pletely between the operations of partial gastrectomy and vagus nerve resection with occasional indications for gastro jejunostomy It is convenient and also correct to consider the surgical treatment according to the type of ulcer en countered because they are aetiologically clinically and pathologically dissimilar

Duodenal ulcer

This is the type of ulcer in which hyperacidity is a marked feature Although duodenal scarring may be present in a patient with achlorhydria the sequence in such cases is usually that the patient had a high acidity in his early years and developed a duodenal ulcer Later as a result perhaps of gastritis or some degenera tive change in the mucosa the acidity diminished and the ulcer healed leaving a scar It is almost unknown to have a proven achlorhydria and an active duodenal

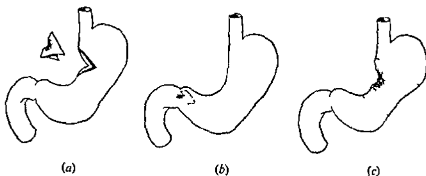


FIG 168 —Operations for the local excision of ulcer now considered inadequate as elective procedures (*a*) Wedge excision (*b*) local excision and (*c*) sleeve resection

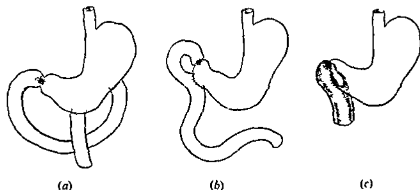


FIG 169 —By passing operations for duodenal ulcer (*a*) Gastro jejunostomy (*b*) gastro duodenostomy and (*c*) pyloroplasty

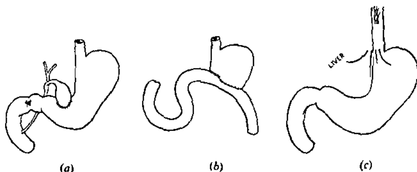


FIG 170 —Some attempts to lower the gastric acidity surgically (*a*) Cholecyst gastrostomy (*b*) partial gastrectomy and (*c*) vagotomy

ulcer Now the jejunal mucosa appears to have even less resistance to the erosive effects of the gastric secretions than the duodenum and so if the operation of gastro jejunostomy is performed although the duodenal ulcer may and practically always does heal perfectly complicating ulceration near the gastro jejunal suture line or in the proximal jejunum of the efferent loop occurs in as many as 30 per cent or more of the cases Not all of these 30 per cent suffer enough to justify further surgery but they all suffer from periodic bouts of dyspepsia and many suffer ulcer complications such as perforation haemorrhage stenosis or fistula formation There are types of cases in which gastro jejunostomy may be a fully justifiable operation however One is the occasional case of duodenal ulceration associated with a low or moderate acidity In such cases the ulcer is usually not very active and symptoms due to obstruction or resulting from severe duodenal scarring are more prominent than those due to active ulceration The lowered acidity in these cases may follow gastritis which results from chronic duodenal obstruction and gastric stasis or it may be due to non obstructive gastritic or degenerative change in the mucosa In the former case there is always some risk of recurrent ulceration for gastritis due to duodenal obstruction may be improved by the gastro jejunostomy and the acidity may rise again Another type of case is the patient who has severe symptoms from a duodenal ulcer penetration stenosis or recurrent bleeding but yet who is so aged or fragile that gastrectomy is considered an unjustifiable risk In such cases a gastro jejunostomy may be done and the 30 per cent risk of anastomotic ulceration must be taken Not all of the 30 per cent will have severe trouble from the stomal ulcer and many even of those who have symptoms of stomal ulceration will be grateful for their operation

Partial gastrectomy for duodenal ulcer has steadily increased in popularity with the rise in the incidence of stomal ulceration following gastro jejunostomy (or it may be an increasing awareness of the incidence of stomal ulceration) and the steadily lowering mortality from the operation of gastrectomy Fifteen to twenty years ago the mortality in good hands was in the region of 10 per cent nowadays it is 1 to 2 per cent in the same hands and sometimes less Partial gastrectomy has the advantage of being a long tried and tested procedure with a mortality which compares favourably with the natural risks of the disease There is a high chance in the region of 97 per cent of freedom from further peptic ulceration About 80 per cent of the cases lose all sense of having had ulcer trouble and are able to resume full work (Tanner 1948) It has some disadvantages There still is an operative mortality and some operative morbidity It is time consuming requiring from 6 weeks in the young to up to 12 weeks in those over 50 before full fitness for work is regained A small percentage of patients may develop post cibal symptoms of epigastric feelings of distension or dizziness sweating and fatigue A smaller percentage develop iron deficiency anaemias and many remain too slender for their liking

Technique of gastrectomy for duodenal ulcer

Broadly speaking the gastrectomy may be completed either by a gastro duodenal anastomosis (Billroth I Fig. 171 (*a*)) or gastro-jejunal anastomosis (Polya Fig 171 (*b*)) Although the Billroth I result superficially resembles a normal

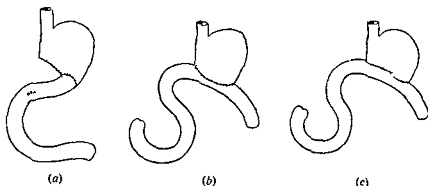


FIG 171 —Methods of reconstruction after partial gastrectomy (*a*) Gastro duodenal anastomosis (Billroth I) (*b*) gastro j junal anastomosis (Polya) and (*c*) valved anastomosis

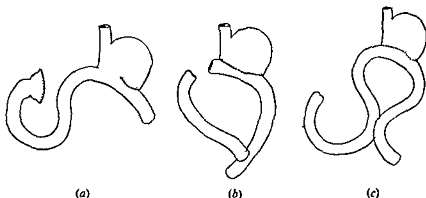


FIG 172 —Unsatisfactory operations for ulcer (*a*) Partial gastrectomy pre serving the pyloric end of the stomach (*b*) Roux loop anastomosis following partial gastrectomy (this diverts all the biliary pancreatic and duodenal secretion from the residual stomach) and (*c*) short-circuited loops after gastrectomy (this may divert all or part of the biliary pancreatic and duodenal secretion from the residual stomach)

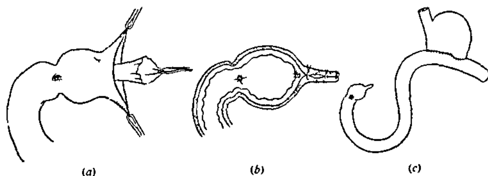


FIG 173 —Plenk s modification of partial gastrectomy with pre pyloric section and exenteration of the pyloric antral mucosa

stomach and has the undoubted advantage of more normal post operative duodenal function and no jejunal loops to give rise to occasional complications it has three disadvantages

It involves utilizing a diseased organ for the anastomosis To make the anastomosis pass the ulcerative lesion in the duodenum may involve a lengthy and perhaps hazardous dissection of the duodenum It is difficult to be quite sure that small ulcer scars do not remain in the part of the duodenum retained

There is a tendency in some cases to restrict the extent of the gastric resection in order to obtain a tension free gastro duodenal anastomosis

Recurrent ulceration is very difficult to diagnose after this form of resection and relatively minor degrees of stomal ulceration may lead to gastric retention

Most surgeons therefore prefer a gastro jejunal anastomosis after gastrectomy for duodenal ulcer Many variations of the operation are described most of which give excellent results There is a general consensus of opinion that the afferent loop no matter whether an antecolic or retrocolic anastomosis is made should be as short as possible both because short loops diminish the chance of obstruction due to kinking or stasis in the loop and because the tendency to jejunal ulceration appears to increase the farther down from the pylorus the stoma is formed Some surgeons utilize the whole cut end of the stomach for the anastomosis some close part of the cut end (Fig 171 (c)) to produce the so called Hofmeister valve The writer s opinion is that the whole width of the stomach gives an un necessarily wide stoma it increases the chance of gastric contents entering the afferent jejunal loop and as it is simpler and he believes safer to use only ½ or ⅓ of the diameter of the stomach for the anastomosis a Hofmeister valve is preferred

Certain difficulties in duodenal resection have led to interesting and very instructive results and developments of the operation The dissection of a quiescent duodenal ulcer lying near to the pylorus may be a very simple matter but if the ulcer is actively penetrating the pancreas over a wide area dissection may be extremely difficult and at times the pancreatic and bile ducts have been opened or difficulty experienced in closing the duodenum In such cases a poor duodenal closure may result in the duodenal sutures giving way with the production of either a general peritonitis or duodenal fistula both very lethal complications Therefore it was suggested (Ogilvie 1935) that as the secretion of the gastric antrum was alkaline there could be no harm in transecting the stomach 5-6 centimetres proximal to the pylorus in these difficult cases closing the antrum and then proceed to a high gastrectomy removing much of the acid secreting mucosa of the body (Fig 172) This operation was followed by a very high incidence of stomal ulceration (Ogilvie 1938) 40 per cent or more The tendency to stomal ulceration could be arrested by early re operation to remove the pyloric antrum Therefore a modification of pre pyloric section was recommended whereby after pre pyloric section through the serous and muscular coats of the stomach the antral mucosa was dissected out as far as the pylorus and there transected and removed The seromuscular coats of the antrum were retained and with them the closure was completed by one of several excellent methods for example Finsterer Bancroft or Plenk This operation was not followed by stomal ulceration and is valuable for the very difficult case (Fig 173) Unfortunately in some cases the extreme difficulties of a duodenal dissection are not always recognized until the

duodenal dissection has been started and perhaps the penetrating ulcer separated from the invaded organ and perforated completely Another modification particularly to be recommended to the less experienced surgeon or for dealing with a poor risk case is to perform a pre pyloric section retaining the antral mucosa followed by high gastrectomy as a first stage Six to eight weeks later a second operation is performed (usually through a high right transverse incision) to remove the antrum The six weeks rest from activity in the duodenum will nearly always have led to complete ulcer healing and the tissues will be less oedematous and inflamed (Fig 174) Removal of the antrum at this stage may be a very simple procedure and is rarely difficult It is well not to wait longer in order to see if the patient develops a recurrent ulcer for they appear early the writer having seen one in such a case within six weeks of the antrum conserving gastrectomy Furthermore such stomal ulcers may be quiescent or be heralded with a severe complication such as perforation haemorrhage or fistula

An alternative method of dealing with the problem of the difficult duodenal ulcer is by vagal nerve resection

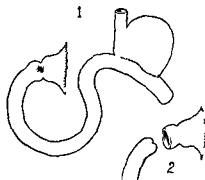


FIG 174 —Two stage gastrectomy for severe duodenal ulcer the antrum being removed at the second stage

Vagotomy

It has been known for many years that vagal section would diminish the gastric acidity and gastric tone Early trials of vagotomy were given up because of the unpleasant side effects which were produced and which persisted in about half of the cases During the last 5–6 years many thousands of vagotomy operations have been performed and the effects have been studied in some detail The operation was expected to reduce the appetite juice but was found to reduce not only the acid secretion following the ingestion of food but also the basal day and night secretion of juice In addition disturbances of gastric motility were noted Tone was diminished peristaltic waves incomplete and the emptying time of the stomach was delayed in some cases to over 24 hours In most of the cases there is a tendency for the peristaltic activity and tone of the stomach to improve in the course of time usually between 6–12 months The extent to which gastric acidity may return to normal is indefinite Another effect of vagotomy is temporary dysphagia due to a condition radiologically resembling cardiospasm (Fig 175) This usually returns to normal within a few weeks at the most though whether there will be any very late effects must remain undecided for a few years Similarly there may be temporary disturbances of small intestinal motility with production of severe post operative ileus and later of diarrhoea

Clinically the vagotomy appears to exert a beneficial effect on the ulcer insofar as ulcer pain is immediately relieved in nearly all the cases though after 6 months some cases relapse That the pain relief is due not merely to division of sensory nerve fibres is suggested by the fact that shortly after the vagotomy but before the ulcer is healed ulcer pain can be reproduced by injecting a solution of deci normal hydrochloric acid into the stomach The pain relief is thus presumably due to the diminished acidity Later ulcer healing usually occurs It has generally been conceded that the ulcer healing resulted from the lowered gastric acidity It is hardly likely that the atony of the stomach is the cause particularly in view of the fact that it is associated with stasis because healing usually persists after vigorous gastric peristalsis is re-established Before long however in more than half of the cases rather distressing symptoms occur Cardiospasm and diarrhoea have been mentioned The former usually settles within a few days Diarrhoea may be severe but it responds well to the administration of non absorbable sulphonamides for example Sulphathalidine Diluted hydrochloric acid (*B P*) 8 millilitres 4 hourly may al o help Most cases settle down completely but in a few instances troublesome diarrhoea may persist after leaving the hospital or there may be a tendency to mild bouts of diarrhoea In addition there may be an epigastric feeling of distension relieved by the eructation of flatus which may have an odour resembling that of rotten eggs This symptom is presumably the result of abnormal gastric digestion of protein that is in the medium of subacidity and gastric stasis In addition there may be symptoms resulting from the gastric stasis for example anorexia epigastric fullness and colic and perhaps vomiting



FIG 175 —Skiagram showing a temporary cardiospasm following vagotomy

duodenal dissection has been started and perhaps the *penetrating ulcer separated* from the invaded organ and perforated completely Another modification particularly to be recommended to the less experienced surgeon or for dealing with a poor risk case is to perform a pre pyloric section retaining the antral mucosa followed by high gastrectomy as a first stage Six to eight weeks later a second operation is performed (usually through a high right transverse incision) to remove the antrum The six weeks rest from activity in the duodenum will *nearly always have led to complete ulcer healing and the tissues will be less* oedematous and inflamed (Fig 174) Removal of the antrum at this stage may b a very simple procedure and is rarely difficult It is well not to wait longer in order *to see if the patient develops a recurrent ulcer for they appear early the writer* having seen one in such a case within six weeks of the antrum conserving gastrec tomy Furthermore such stomal ulcers may be quiescent or be heralded with a severe complication such as perforation haemorrhage or fistula

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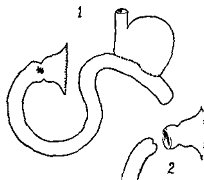


FIG 174—Two-stage gastrectomy for severe duodenal ulcer the antrum being removed at the second stage

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is preferable or even essential first to confirm the true nature of the lesion and secondly in order to perform an additional operation to combat gastric stasis—sometimes termed a drainage operation Excellent views of the nerves may be obtained by the abdominal route and 5-6 centimetres of each nerve can be removed without difficulty The nerves in some 90 p r c nt of cases form two discrete trunks in the region of the cardia The nerves may also be seen to be dividing into terminal branches in this neighbourhood and the recognition of these branches increases the chance of complete vagal division (Fig 176)

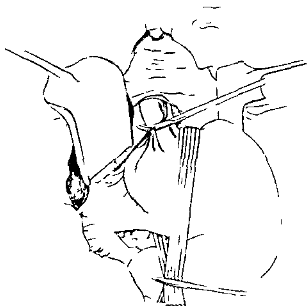


FIG 176—Displaying terminal branches of the anterior vagus nerve prior to resection of a length of the nerve

Vagotomy must necessarily remain an operation of undetermined value for several more years It is possible that there may be a rise to normal acidity even after several years with recurrence of ulcer symptoms though in some cases it is found that after 2-3 years the gastric acidity diminishes still further Other possible late effects are the development of iron deficiency anaemia as a result of the sub acidity or late oesophageal troubles from the partial denervation of the cardia region As results after 3-4 years are reasonably favourable it may be surmised that of the patients who have been relieved for 3 years even a rise to normal acidity would lead to breakdown of the ulcer in only a minority of them

Gastrectomy or vagotomy for duodenal ulcer

The indications for the use of gastro jejunostomy have been described The controversy ranges over the relative advantages of gastrectomy and vagotomy

of food eaten many hours previously These symptoms may be rendered less urgent by preventing over distension of the stomach by continuous gastric aspiration in the early post operative days and by ordering the patient to take small dry meals afterwards When gastric tonus returns and autonomous peristaltic activity and emptying is established most or all of the gastric stasis symptoms tend to dis appear though in some the symptoms persist and may still be present two years and more after vagotomy

These side effects have been so severe that the operation of pure vagotomy for duodenal ulcer has been largely abandoned Instead vagotomy is combined with various additional procedures Gastro jejunostomy was the first used and later various forms of pyloroplasty and partial gastrectomy all of which were efficient in preventing gross gastric stasis and so eliminating much of the epigastric fullness and foul belching associated with the condition Time will show which of these procedures is the best It may even be that eventually a Rammstedt type of pylorotomy may be found sufficient in the absence of gross duodenal stenosis Gastro jejunostomy has the disadvantage of introducing the possibility of stomal ulceration and it also causes a greater degree of small bowel ileus in the immediate post operative period Partial gastrectomy when combined with vagotomy not unexpectedly leads to a greater morbidity and if carried out widely would probably lead to a higher mortality Some of the cases develop both post vagotomy and post gastrectomy gastro intestinal symptoms It has been recommended and practised by some that only a low gastrectomy a pyloric antrectomy should be carried out However there is not much difference in the risk of a high and low gastrectomy for duodenal ulcer for most of the work and risk concerns the duodenal closure The writer s present impression of this combination is that in 97 per cent at least the vagotomy forms an unnecessary adjunct to the high gastrec tomy It is better to perform the one operation favoured either gastrectomy or vagotomy plus pyloroplasty and retain the second as a means of dealing with the small percentage of stomal or persistent ulcers

How pyloroplasty succeeds in preventing post vagotomy effects is uncertain a simple Heineke–Mikulicz procedure appears to suffice The essential feature of the pyloroplasty is to transect the pylorus rather than the ulcer scar because cases of the grossest delay will be encountered after vagotomy in which there is no appreciable narrowing of the duodenum by the ulcer scar and yet pyloroplasty restores the gastric evacuation rate to normal Because pyloroplasty itself has very little long standing success in the treatment of duodenal ulcer its addition does not confuse the results of vagotomy as may occur when two curative operations are combined Furthermore if the duodenal ulcer recurs or persists it is not so difficult to perform a gastrectomy in the presence of a pyloroplasty as it is in the presence of a gastro jejunostomy

Technique of vagotomy

There has been a good deal of discussion on the relative merits of the trans thoracic or abdominal routes for the performance of vagotomy A wider resection of nerve fibres is possible by the transthoracic route but some cases are com plicated by post operative intercostal neuralgia which leads to as much pain as the original ulcer However the general opinion now is that the abdominal route

of post gastrectomy post cibal symptoms and of secondary anaemia The latter complications are rarely of any great severity though the mortality rate is higher than that resulting from operation for duodenal ulcer probably because the patients are on the average older and more debilitated by the lesion Therefore it may be said that although there are rare indications for palliative operation in dealing with certain complications of chronic gastric ulcer the only operation to be considered in elective surgery is partial gastrectomy

The form of gastrectomy that is whether it be completed by gastro duodenal or gastro jejunal anastomosis (Fig 171) is not of great moment The advantage of the former in the absence of a complicating duodenal ulcer is that it is a some what simpler operation involves no jejunal manipulation and leaves no possibility of jejunal loop troubles The operative result resembles more the normal anatomi cally and physiologically and post cibal or dumping symptoms are less frequent and usually milder than those which may follow the Polya operation Its dis advantage is that gastric evacuation is occasionally delayed in the immediate post operative period and very rarely late stomal obstructive symptoms may occur

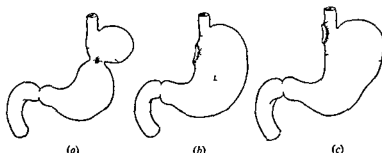


FIG 177—Resection of high gastric ulcer Line of gastric transection recom mended in cases of (*a*) hour glass deformity (*b*) high lesser curve ulcer and (*c*) ulcer at the cardia

though if a wide stoma is made the latter should be almost non existent A Polya anastomosis is usually easier and freer of tension after a high gastrectomy except in patients with very lax viscera At present the Billroth I operation is increasing in popularity in the treatment of gastric ulcer but there is little to choose between the two operations on the whole

The rationale of gastrectomy and the cause of its success in the treatment of gastric ulcer is not easy to understand The reduction in acidity may play a part but many of the cases have subacidity before the operation The removal of the scarred area is an advantage too but a gastrectomy leaves a long linear scar Possibly the alteration in the relationship between the food level in the stomach before and after operation plays a part in the changed susceptibility to ulceration

Various complicating factors in the chronic ulcer may be encountered Deep penetration of the ulcer into a neighbouring organ usually pancreas liver or mesocolon may be dealt with by pinching off the ulcer that is squeezing the tissues between stomach and invaded organ firmly between finger and thumb The two usually separate at the line of adhesion where it is avascular and so the

in the treatment of duodenal ulcer The mortality of vagotomy is as low as and probably lower than that of gastrectomy for duodenal ulcer Figures can be given to prove that either have the lower mortality but a general review suggests that vagotomy carries less risk in expert hands provided that there is every facility for correct post operative care

Either operation will give a 3 5 year cure rate of over 90 per cent and both have occasional untoward sequelae Some surgeons have endeavoured to decide which operation to perform according to the response to the insulin test or fractional test meal This is not a very good guide for neither is a quantitatively accurate test of vagus or of peptic secretory activity A better weight is maintained after vagotomy than gastrectomy in the average case and so there is some justification for using vagotomy for the young in their growing years when nutritional deficiency may retard normal growth The patients most prone to anastomotic ulceration after gastro jejunal anastomosis are the younger patients with a high gastric acidity rapidly emptying and perhaps steerhorn type of stomach This type of case may legitimately be chosen for vagotomy One could not quibble at vagotomy combined with gastro jejunostomy or pyloroplasty being preferred in a case where the duodenal ulcer was extensive and penetrating and presented grave difficulties for resection The highly strung patient whose discomfort from his ulcer reflects the ups and downs of his anxieties is again a type of case in which there is some justification for dividing the nervous pathway which on stimulation increases gastric secretory activity The association of a gastric ulcer or scar with the duodenal ulcer contra indicates vagotomy for there is no sound evidence that vagotomy will cure or even prevent the development of gastric ulcer

For the general run of case no one can give a reliable opinion as to which is the better operation to carry out for we lack knowledge of the long term results of vagotomy

Gastric ulcer

Gastric ulcer presents a different problem from that of duodenal ulcer Hyper acidity is not a typical feature of gastric ulcer although occasional cases are associated with hyperacidity and on the average the gastric acidity is lower than normal Not infrequently a resistant chronic ulcer is seen in an achlorhydric or almost achlorhydric gastritic mucosa and in such cases it appears that the ulcer is due to local disease or lack of healing power rather than to a high digestive power of the peptic juice

In earlier days local resection operations were practised but have been abandoned because of the high relapse rate Combination of resection with gastro jejunostomy may be effective in some pre pyloric ulcers Stomal ulceration is rare when gastro jejunostomy is performed for gastric ulcer but recurrence or per sistence of ulceration particularly if the ulcer affects the body of the stomach is common Partial gastrectomy has for many years been the most satisfactory opera tion for the condition Stomal ulceration after gastrectomy for gastric ulcer is excessively rare in my own series of well over 600 gastrectomies for simple gastric ulcer no case of anastomotic ulcer has occurred nor have I seen such an occurrence following operations of this nature performed by any of my surgical colleagues The risks to be faced are therefore the primary mortality and morbidity the risk

In the treatment of stomal ulceration following gastrectomy it must be emphasized that plastic procedures to the stoma are of no avail The effective procedures are higher partial or total gastrectomy or vagotomy or a combination of both Before vagotomy was widely used a higher gastrectomy was usually practised In some such cases further ulceration occurred and for this total gastrectomy or better still quasi total gastrectomy leaving a small about ½ centimetre fringe of gastric mucosa attached to the oesophagus was used However vagotomy seems to be very effective in these cases and total gastrectomy should practically never be required With a minimally scarred stoma vagotomy alone should suffice If scarring is severe particularly if there is afferent or efferent loop obstruction or there is deep penetration of the ulcer a slightly higher resection making a fresh stoma is advisable in addition to the vagotomy

If an operation which is particularly prone to produce anastomotic ulceration has been performed this must be corrected For example if a Roux gastro jejunostomy (Fig 172) or gastro jejunostomy with short circuiting of the afferent and efferent loops has been performed this must be corrected in order to make the biliary and duodenal juices pass over the stoma again If a gastrectomy has been performed but the antrum and its mucosa left behind then the result of simple antral resection should be studied before proceeding to any further procedure

In cases where a gastro colic fistula complicates the picture it is helpful to perform a proximal colostomy at the hepatic flexure or ascending colon prior to dealing with the fistula

Oesophageal ulcer

Oesophageal ulcer most commonly results from a reflux oesophagitis in which regurgitation of gastric juice up the oesophagus leads to inflammatory erosive haemorrhagic and sometimes deeper ulcerative lesions Rarely the lower oesophagus may in fact be lined with gastric mucosa and an ulcer may appear in this so called ectopic gastric mucosa or mediastinal stomach Such cases are really more allied to gastric ulcer (Barrett 1950)

Reflux oesophagitis may result from incompetence of the cardiac sphincter or valve mechanism which may be primary or result from hiatus hernia or congenital short oesophagus It may be post operative as a result of oesophago gastric anastomosis or cardioplasty performed in the treatment of cardiospasm or stricture or it may follow resection of the cardiac end of the stomach followed by oesophago gastric anastomosis

Whatever the cause the main operative treatment should be aimed at eliminating reducing or neutralizing the regurgitating gastric juice If present a hiatus hernia may be repaired If this is impracticable or if there is no hiatus hernia the alternative procedures are either lower partial gastrectomy of the Polya type that is removing the distal two thirds of the stomach which reduces and neutralizes the gastric secretion or total gastrectomy (Fig 178) Vagotomy is under trial and is certainly not always successful In the post operative cases it is usually hazardous to undo a cardioplasty or oesophago gastric anastomosis and the other alternative procedures are high Polya partial gastrectomy or total gastrectomy Upper partial gastrectomy (cardio oesophagectomy) which has been

invaded organ is not damaged by the separation The ulcer floor in the invad d organ requires no treatment and must not be cauterized or excised Occasionally sharp dissection is required to separate the ulcer edge in the stomach from its base in the invaded organ

If the ulcer is high some variation in technique is required If high and stenosed—an hour glass deformity the line of gastric section should be just above the stenos d area, *but as much stomach as is healthy* above the stenosis should be conserved—there is no risk of stomal ulcer (Fig 177 (*a*)) In other cases it is usually possible to shape the transection line so as to skirt the ulcer—the Pauchet modification in which a tongue shaped piece of the lesser curve containing the ulcer should be removed (Fig 177 (*b*)) If the ulcer is at the cardia or juxta cardiac and malignancy can be reasonably excluded then a partial gastrectomy below the ulcer (Fig 177 (*c*)) may be performed This gives a good chance of ulcer healing and of freedom from further ulceration but healing should be confirmed before allowing the *patient to resume his work*

Anastomotic ulcer

Anastomotic ulceration may follow when the stomach is anastomosed to the jejunum duodenum or oesophagus The majority of such ulcers arise after gastro jejunostomy or much more rarely after gastrectomy for duodenal ulcer Occasional cases follow gastric anastomosis for non ulcerative lesions for example congenital pyloric stenosis (Walters 1946) or cardiospasm (Barrett and Franklin 1949) *Gastro oesophageal stomal ulcers may follow resection of the upper stomach* and will be considered under oesophageal ulcer

The choice of operation for dealing with stomal ulcer after gastro jejunostomy lies between the following

Restoration of the normal anatomy that is dismantle the stoma repair or resect the jejunum according to the extent of the scarring and repair the stomach This operation has had a poor reputation in the past because of the tendency fo the original duodenal ulcer to recur Therefore this must be completed by per *forming a vagotomy and pyloroplasty*

Dismantling the stoma and performance of a high partial gastrectomy

Simple vagotomy

Vagotomy combined with gastrectomy

The first is suitable for patients who have severe stomal ulceration together with nutritional defects or the dumping syndrome but is still under trial in view of its reliance on the vagotomy

The second method gastrectomy is the most well tried and generally satis factory procedure and is suitable for the majority of cases

Simple vagotomy alone may be used if gastro jejunal scarring is minimal *More* reports of this operation will be required before one can give a sound opinion as to its reliability

Vagotomy combined with gastrectomy would be advisable if one assumes that the recurrent ulceration is of an extremely vicious type but not all cases *are* resistant to treatment and it would seem wiser to confine the operation to gastrectomy and perform vagotomy in the minority of cases that ulcerate again

gastric lavage with a weak saline solution and by emptying the stomach 3 hours after the last meal of each day Changes in the blood chemistry and dehydration resulting from chronic pyloric stenosis will be treated usually by daily intra venous saline and glucose solutions

The second object is to get the ulcer into as quiescent a state as possible Particularly in the case of duodenal ulceration it may be necessary to put sutures into the duodenum within a centimetre beyond the ulcer crater edge If the ulcer is quiescent and fibrotic the sutures will hold well if the ulcer is active and the duodenum oedematous and inflamed suturing is less secure

The third and perhaps most important object is to make the patient nutritionally and physically as fit as possible Many are starved and exhausted by lack of sleep pain and anxiety A high protein diet should be given because hypop oteinaemia will diminish the wound healing powers of the body As some patients are on the verge of vitamin deficiency and may indeed be precipitated into an acute deficiency as a result of an operative trauma the diet should be supplemented by a full course of vitamins particularly the B complex and C Adequate sleep and rest for a large part of the day should be ensured for a minimum of a week prior to operation General gentle exercises to prevent phlebothrombotic complications are helpful and must be continued after operation Lung complications will be diminished if the patient abandons smoking at least a week before the operation and is given a course of respiratory exercises Before operation is carried out it is advisable to ensure that the blood protein nitrogen and sugar levels are within normal limits

To sum up it may be said that the best preparation for operation is a good course of medical treatment for the ulcer One of the reasons for the diminishing mortality following operations on the stomach is undoubtedly the care taken in preparing the patient and this preparation must not be half hearted

Post-operative care is concerned first of all with preventing dehydration or anaemia In most cases this can be effected by mouth feeding fluids being taken by most patients in adequate amounts within twenty four hours of operation If prolonged gastric suction becomes necessary the intravenous administration of saline solution will be necessary If there is much gastric juice being aspirated 500 1 000 cubic centimetres of normal saline may be required daily the rest of the fluid being given as a weaker saline solution for example 0 18 per cent saline solution made isotonic with glucose Excessive blood loss during operation should be corrected by blood transfusion during operation but further transfusion may be required after operation

In most cases oral feeding can be instituted rapidly semi solids being taken by the third day Such semi solids should contain protein for example egg milk or amino-acid concentrates and adequate vitamins should be included

Respiratory and general trunk and limb exercises are continued post operatively until the patient is ambulant

POST-OPERATIVE COMPLICATIONS AND THEIR SEQUELAE

When considering the advisability of recommending surgery one must bear in mind the possibility of post-operative complications and the influence they may have on the patient s subsequent life

followed by oesophageal ulceration should be treated by conversion to a total gastrectomy preferably of the Roux type (Fig 179)

Of these procedures it is wisest to try the simpler first *Partial gastrectomy* of the Polya type (lower partial gastrectomy) in the treatment of oesophageal ulcer is advocated by Wangensteen (1949) but it is not an established method as it is still under trial If this fails it is not very difficult to convert it to a Roux total gastrectomy by the abdomino thoracic route

Gastrostomy or jejunostomy is occasionally required in severe cases of penetrating or stenosed oesophageal ulcer When stenosis is severe repeated dilatation with gum elastic bougies may be required

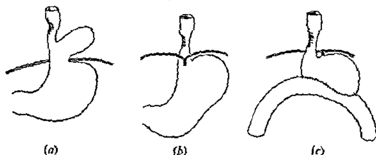


FIG 178 —Methods of dealing with peptic oesophagitis or oesophageal ulcer (*a*) and (*b*) repair of hiatus hernia and (*c*) lower partial gastrectomy

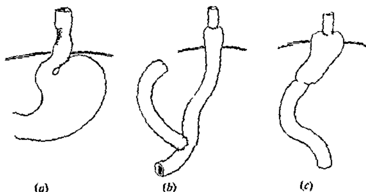


FIG 179 —Further methods of dealing with peptic oesophagitis or oesophageal ulcer particularly the post-operative type (*a*) Peptic oesophageal ulcer following oesophago gastric anastomosis (*b*) end to-end *oesophago-jejunostomy* (with or without total gastrectomy) and (*c*) extensive upper partial gastrectomy (*oesophago-gastrectomy*)

CARE OF PATIENTS BEFORE AND AFTER ELECTIVE OPERATION FOR PEPTIC ULCER

The pre operative preparation has a threefold object The first is to overcome the effects of any ulcer complication Chronic anaemia due to slow bleeding is corrected by the administration of iron and if necessary by blood transfusion Long standing obstruction of the stomach or duodenum is dealt with by daily

gastric lavage with a weak saline solution and by emptying the stomach 3 hours after the last meal of each day Changes in the blood chemistry and dehydration resulting from chronic pyloric stenosis will be treated usually by daily intra venous saline and glucose solutions

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POST-OPERATIVE COMPLICATIONS AND THEIR SEQUELAE

When considering the advisability of recommending surgery one must bear in mind the possibility of post operative complications and the influence they may have on the patient s subsequent life

Post operative phlebothrombosis with its complications of *deep femoral thrombosis and embolism is not in Great Britain a very common complication of interval operations for ulcer, and most commonly affects the patient who already has post operative intestinal or infective complications The incidence is much less common than that following operation on the lower abdomen*

Pulmonary complications are the most serious risk after interval operations on the stomach and duodenum although their dangers have diminished as a result of improved chemotherapy and their incidence with prophylactic chemo therapy better anaesthesia and post operative chest exercises Occasional late sequelae may result for example bronchiectasis after pulmonary collapse and infection, or diminished function of the thoracic cage following empyema

Abdominal complications are now seldom experienced Duodenal leakage can usually be prevented by careful duodenal closure and if it occurs its seriousness concerns its immediate dangers rather than late sequelae The chance of stomal ulceration and complications arising from this are always to be carefully considered *The risks of wound infection and subsequent herniation vary according to the type of incision used but post-operative hernia of the upper abdomen is less incapacitating and dangerous than in the lower or mid abdomen Other very rare intestinal complications are strangulation or obstruction by a peritoneal band or adhesion obstruction of long loops internal herniation through the mesocolon or round bowel loops and prograde or retrograde jejuno gastric intussusception There is reason to suspect that the risks of biliary disease and of pancreatitis are greater in the gastrectomized patient than in the average person*

Post operative achlorhydria may lead to an iron deficiency anaemia Very rarely severe vitamin B or general nutritional deficiencies are seen Iron and vitamin deficiencies are readily corrected but general deficiencies may prove very obstinate to treat particularly if associated with diarrhoea

POST OPERATIVE SYMPTOMS AND RESULTS

More common than the very rare intestinal complications just recorded are certain specific sequelae of gastric operations

The dumping syndrome or gastrectomy post cibal symptoms are described elsewhere (page 465) It is commoner and more severe following the gastro jejunal forms of reconstruction particularly if the afferent loop is long than after the gastro duodenal reconstruction (Mimpriss and Birt 1948) It occurs at times after simple gastro jejunostomy In a series of 97 followed up by the writer some degree of this symptom was notable in 7 per cent of the cases after 5 years (Tanner 1948) It is to be noted too that milder degrees of the syndrome heat flushing epigastric fullness palpitations and drowsiness may be noted in normal people after taking an abnormally heavy meal and more severe degrees may occur as a form of nervous dyspepsia The general advice is to treat the lesion by small frequent meals but the writer believing that the body mechanism can adapt itself given time believes in preventing or treating the lesion by recom mending the patient to take good sized meals particularly of protein and fatty foods as soon as possible after operation even though at first a feeling of dis tension is provoked

Post vagotomy symptoms occur to some degree in the majority of patients who

undergo simple vagotomy and in 25 to 30 per cent the symptoms may still be severe at the end of a year The main features have already been discussed bloated feelings in the epigastrium eructations often of foul smelling gas abdominal cramps rarely vomiting and diarrhoea Seldom are complaints of faintness and vasomotor disturbances made The symptoms may be diminished by avoiding overloading of the atonic stomach in the post operative period and later small dry meals should be recommended with periods of starvation or gastric lavage for severe exacerbations The diarrhoea may be diminished by the use of Sulphathalidine or other effective intestinal antiseptic and a mixture containing diluted hydrochloric acid to be taken with meals is also helpful Cases of persistent severe diarrhoea are recorded but in the writer s experience only one such case was troublesome after a year and complete relief followed a gastro jejunostomy for gastric stasis Milder degrees are more common and may persist

The severity of post vagotomy symptoms has caused many surgeons to abandon the pure vagotomy operation and instead they now combine it with pyloroplasty gastro jejunostomy or gastrectomy

The general prognosis of the patient operated on for peptic ulcer will vary according to the nature of the operation performed Actuarial studies have been carried out on patients surviving operation for duodenal ulcer which show that their life expectation is slightly greater than that of the general population Similar studies of patients surviving operation for gastric ulcer have been confused by the fact that in the gastric ulcer series a certain number of cases are included which were in fact carcinomas (Eusterman and Balfour 1935) Over 90 per cent of the patients who have a gastrectomy for gastric or duodenal ulcer or a vagotomy combined with drainage for a duodenal ulcer will be satisfied with their operation and free of recurrent ulcer symptoms In a high percentage of the cases the patient eventually loses his ulcer or stomach consciousness and is able to forget that he ever had a peptic ulcer

REFERENCES

Barrett N R (1950) *Brit J Surg* 38 175
— and Franklin R H (1949) *Ibid* 37 194
Eusterman C B and Balfour D C (1935) *The Stomach and Duodenum* p 290 Philadelphia Saunders
Martin L and Lewi N (1949) *Lancet* 2 115
Mimpriss T W and Birt St J M C (1948) *Brit med J* 2 1095
Ogilvie W H (1935) *Ibid* 1 457
— (1938) *Lancet* 2 295
Tanner N C (1948) *W Lond med J* 53 35
Walters W (1946) *J Amer med Ass* 131 12 69
Wangensteen O H (1949) *Surg Gynec Obstet* 88 560

Post operative phlebothrombosis with its complications of deep femoral thrombosis and embolism is not in Great Britain a very common complication of interval operations for ulcer and most commonly affects the patient who already has post operative intestinal or infective complications The incidence is much less common than that following operation on the lower abdomen

Pulmonary complications are the most serious risk after interval operations on the stomach and duodenum although their dangers have diminished as a result of improved chemotherapy and their incidence with prophylactic chemo therapy better anaesthesia and post operative chest exercises Occasional late sequelae may result for example bronchiectasis after pulmonary collapse and infection or diminished function of the thoracic cage following empyema

Abdominal complications are now seldom experienced Duodenal leakage can usually be prevented by careful duodenal closure and if it occurs its seriousness concerns its immediate dangers rather than late sequelae The chance of stomal ulceration and complications arising from this are always to be carefully considered The risks of wound infection and subsequent herniation vary according to the type of incision used but post operative hernia of the upper abdomen is less incapacitating and dangerous than in the lower or mid abdomen Other very rare intestinal complications are strangulation or obstruction by a peritoneal band or adhesion obstruction of long loops internal herniation through the mesocolon or round bowel loops and prograde or retrograde jejuno gastric intussusception There is reason to suspect that the risks of biliary disease and of pancreatitis are greater in the gastrectomized patient than in the average person

Post operative achlorhydria may lead to an iron deficiency anaemia Very rarely severe vitamin B or general nutritional deficiencies are seen Iron and vitamin deficiencies are readily corrected but general deficiencies may prove very obstinate to treat particularly if associated with diarrhoea

POST OPERATIVE SYMPTOMS AND RESULTS

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Post vagotomy symptoms occur to some degree in the majority of patients who

was supplemented by a follow up investigation (Illingworth and others 1946) on over 700 cases

The changing incidence of perforated ulcer

There is much evidence to show that during the past 50 years or so a remarkable change has taken place in the incidence of peptic ulcer in the type of ulcer involved and the sex and age of the patients affected For a full review of the early records and literature on this aspect of the subject the reader is referred to the valuable paper by Jennings (1940) Here it will be sufficient to summarize the earlier work while giving in more detail the figures relating to the present time

Reference has already been made to the apparent rarity of perforated ulcer until towards the end of the nineteenth century since then all hospital records agree in showing almost every year a progressive increase in the number of cases treated It is true that the beginning of this rise in frequency coincided with the

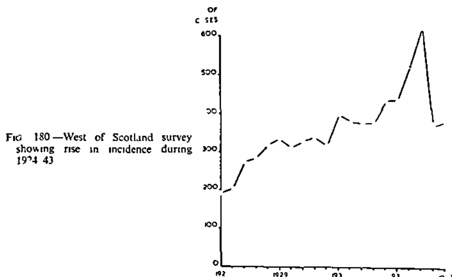


FIG 180—West of Scotland survey showing rise in incidence during 1924 43

introduction of treatment by operation and doubtless part of the apparent increase during the early part of the twentieth century must be ascribed to better diagnosis and readier recourse to hospital but even when due allowance is made for this possible fallacy there can be no doubt that perforation has shown a marked increase in frequency since that time

More recent trends can best be described by reference to our survey in Glasgow which is probably representative of the changes taking place in Great Britain as a whole This survey covered the 20 year period 1924–43 and comprised over 7 000 cases (Fig 180) In 1924 the number treated was 19 by 1938 it had more than doubled the years total being 431 and in the autumn of 1940 a new increase was superimposed rising to a high peak in March 1941 After this remarkably enough there was an equally rapid fall so that by 1943 the annual score was down to less than 400 again

SECTION V

ACUTE PERFORATION

C F W ILLINGWORTH

BY perforation into the peritoneal cavity a peptic ulcer is transformed from a grievous but tolerable burden to a dire calamity The suddenness of the transit and the agonizing intensity of the pain confer a dramatic quality almost unrivalled in human experience and it is not surprising that perforated ulcer has attracted the attention of many observers

The history of the earliest known case is preserved for us not as the report of a new disease (for its nature was not suspected at the time) but by reason of the high rank of the patient She was Henrietta Anne Duchess of Orleans and daughter of Charles I of England who died in 1670 and the story of her fatal illness (*see* Hurst and Stewart 1929) provides a graphic picture of the agonizing course of the disease

Perforation was rare in those days but by the early part of the eighteenth century it was well recognized as a possible cause of sudden death Even as late as 1857 however Brinton was able to collect only 234 cases Since that time the disease has greatly increased in frequency so that in Great Britain perforation ranks second only to appendicitis among acute abdominal disorders

Statistics of incidence

Few diseases in surgical practice lend themselves to epidemiological inquiries of the kind that have been so productive of results in other fields of medical work Perforated ulcer is an exception in this respect for by reason of the accuracy of diagnosis and the almost invariable need for hospital treatment it is possible to obtain reliable data regarding many aspects of its frequency and incidence

Among the earlier papers which have contributed to our knowledge in this way particular attention may be directed to those by Brunner (1903) Caird and others (1913) Bager (1929) and Yudin (1939) Bager s monograph which reviews over 1 700 cases treated in 50 Swedish hospitals over a 15 year period is outstanding by reason of its wide scope and detailed character and gives a complete account of the incidence of the disease at that time

In Great Britain until recently most reports were based upon the experience of individual surgeons or single hospitals and in particular there was no survey of large size based upon the incidence of the disease within a known population To remedy this omission a survey was made a few years ago in the West of Scotland (Illingworth and others 1944 Jamieson 1947) comprising virtually all perforations over a 20 year period in a population of over 2 000 000 The large number of cases surveyed (over 7 000) and the amount of clinical data available produced a mass of useful information in form suitable for statistical analysis This survey

mine the precise situation of an ulcer in the region of the pylorus It is now known that the majority of such ulcers are duodenal but doubtless in the past many of them were described as gastric and even at the present time different surgeons vary in their assessment Only thus can we explain the fact that the proportion of gastric perforations varies greatly even between different hospitals in a single area

Notwithstanding this possibility of error it seems certain that the site incidence of perforation like the age and sex incidence has shown a great change since the turn of the century with gastric perforations formerly predominating but now far outnumbered by duodenal Proof that such a change may take place within a comparatively short time is given in the Glasgow survey where adopting the same criteria throughout in the course of 20 years the proportion of pyloro duodenal to gastric rose from 3 5 1 to 8 1

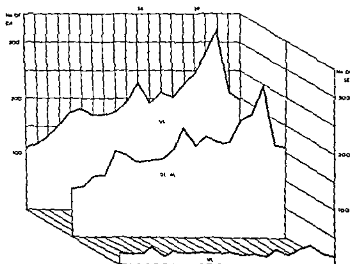


FIG 181 —West of Scotland survey showing comparison of incidence of gastric and duodenal perforations during 1924 43

Detailed studies show that the changing ratio of gastric to duodenal perforations is not due to a decrease in the number of gastric cases which has remained stationary but to an increase in duodenal and indeed in Glasgow the whole of the overall increase in perforations including the war time peak was in respect of duodenal ulcer (Fig 181)

Incidence by month day and hour

Brunner (1903) drew attention to a seasonal incidence in the cases he reviewed which were relatively few in the summer months and relatively numerous in November and December The Glasgow survey by reason of the large number of cases reviewed was able to give precise confirmation of a similar trend and moreover brought to light other short term variations in incidence which hitherto had been unsuspected

War time increase in frequency —During the early war years surgeons in different parts of Great Britain were impressed by the great number of perforations seen at that time Stewart and Winser (1942) then medical students working in London were the first to confirm these impressions by accurate records and they were followed by Rendle Short (1942) in Bristol Wilson (1942) in Liverpool and Riley (1942) in Newcastle The rise in incidence in those cities appeared shortly after air raids began and while the original observers wisely drew no inferences many subsequent writers have been led to conclude that the nervous strain of air bombardment was responsible

By a curious chance the Glasgow survey gave proof that this assumption was incorrect Here the high incidence in 1940–41 synchronized exactly with that observed in other cities but the few serious air raids sustained here came at a later date when the incidence had already reached its maximum

The significance of these changes in incidence since the turn of the century is not yet clear To a large extent they doubtless reflect the changes that have taken place in peptic ulcer as a whole and are to be ascribed to the same causes which may be psychological or perhaps even dietetic The war time peak while not related to actual bombardment may well have been due to the state of nervous strain which pervaded the whole country as a result of the war situation but other factors such as the physical strain of overwork and civilian war duties cannot altogether be exculpated No explanation has yet been offered of the subsequent decline in incidence which became evident in June 1941

Sex incidence

Reports from the literature collected by Brinton (1857) and Brunner (1903) make it clear that until the end of the nineteenth century perforation was predominantly a disease of women who outnumbered men by more than 2 to 1 By 1929 however when Bager s report appeared the distribution had altered radically with men preponderating by 4 to 1 and since that time nearly all reports show a further shift in the sex incidence In the Glasgow survey the proportion was 19 men to 1 woman

In part this change reflects the altered sex incidence of ulcer as a whole but this is not the whole explanation for in non perforated ulcer the proportion is very different In Glasgow for example (the rate differs in other centres) non perforated ulcer affects approximately 7 men to 2 women in other words ulcer is not only less common in women but also much less liable to perforate

Age incidence

The age incidence also has changed completely Until 50 years ago perforation occurred mainly in young people and the medical literature of those days contains many poignant reports dwelling on the tragic character of the disease as it affected young and apparently healthy girls Now on the other hand in both men and women perforation may occur any time from adolescence to old age and the majority are found between 30 and 45 years

Proportion of gastric and duodenal perforations

When we come to study the relative frequency of gastric and duodenal perforations we must remember that at the time of perforation it is often difficult to deter

surveyed this particular detail of clinical history had been recorded with praiseworthy zeal in a large proportion of clinical notes so figures relating to over 1 100 cases were available for study (Fig 184) They confirmed Bager s (1929) and Yudin s (1939) findings that perforation does not take place with equal readiness throughout the twenty four hours It is comparatively uncommon at night while during the day the frequency increases towards noon reaching a higher peak between 4 and 6 p m Bager whose figures were closely similar related this cycle of incidence to the digestive activity of the stomach following the midday meal In the Glasgow survey however Jamieson (1947) has shown that this view is not tenable

The significance of these strange variations in different months on different days and at different hours excites speculation The most probable explanation relates

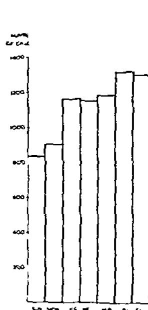


Fig 183 —West of Scotland survey showing incidence by days of the week during 1924–43

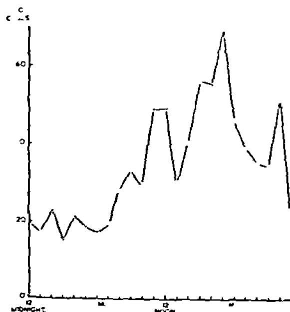


Fig 184 —West of Scotland survey showing incidence by hours during 1924–43

the peaks of incidence of periods of stress while conversely the low figures are related to rest or relief from strain—the holiday season the week-end the night s repose

Geographical incidence —It is well recognized that peptic ulcer as a whole shows great variations in incidence throughout the world being especially common in Western Europe North America and certain parts of India while rare in Africa and most of Asia Although accurate data are lacking it seems that perforated ulcer also shows wide geographic variations and moreover its *incidence does not* always run parallel with non perforated ulcer So far as can be judged both

In this 20 year survey when the figures for corresponding months over the whole period were added together it was seen that in the late summer and autumn months *there was a striking diminution in frequency* while by contrast the frequency at the end of the year was abnormally high (Fig 182) When allowance was made for the differing length of different months, it was found that for the greater part of the year the monthly totals were uniform at about 700 cases each During August September and October the incidence fell abruptly to *the level of about 500 cases The December figure* by contrast rose to the peak of nearly 800

The summer fall might be attributable to climatic factors (though October is not notable for its clemency in the West of Scotland) or to the more plentiful supply of fresh food at this time of the year A more detailed analysis by weeks (Jamieson 1947) *showed that the fall in incidence began to appear in the latter half of July*

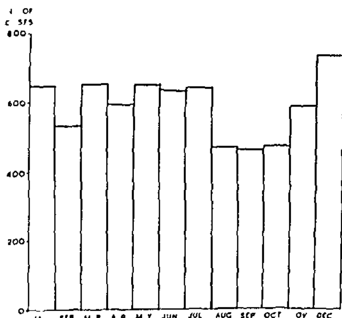


Fig 182 —West of Scotland survey showing incidence by months during 1924 43

which is the annual holiday time for the great majority of the population in this area and suggested the possibility *that this period of rest and recreation* was responsible by conferring a measure of immunity during the subsequent months It was suspected that the December rise might be related to the seasonal festivities but detailed analysis disproved this suggestion

Pursuing the analysis further the cases were divided up according to the day of the week on which the perforation occurred This brought to light the surprising discovery that perforations do not occur with equal frequency throughout the week but increase in number as the week proceeds (Fig 183) Sunday and Monday gave the lowest figures Tuesday *Wednesday and Thursday intermediate scores* while the highest totals were on Fridays and Saturdays

The final step in this series of analyses was to group the figures according to the hour at which perforation took place It was fortunate that in one of the hospitals

surveyed this particular detail of clinical history had been recorded with praiseworthy zeal in a large proportion of clinical notes so figures relating to over 1 100 cases were available for study (Fig 184) They confirmed Bager s (1929) and Yudin s (1939) findings that perforation does not take place with equal readiness throughout the twenty four hours It is comparatively uncommon at night while during the day the frequency increases towards noon reaching a higher peak between 4 and 6 p m Bager whose figures were closely similar related this cycle of incidence to the digestive activity of the stomach following the midday meal In the Glasgow survey however Jamieson (1947) has shown that this view is not tenable

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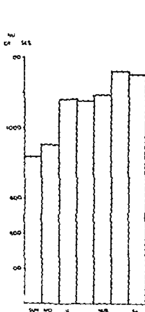


Fig 183 - West of Scotland survey showing incidence by days of the week during 1924 43

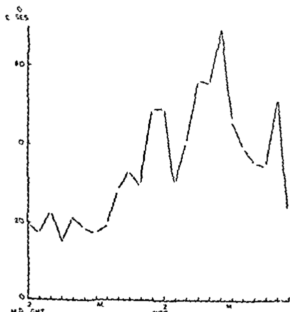


Fig 184 —West of Scotland survey showing incidence by hours during 1924-43

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perforated and non perforated ulcer are about as common in Scandinavia as in Great Britain In North America while the incidence of non perforated ulcer is known to be high perforation appears to be less frequent Even more marked is the disparity in South India where as Somervell (1942) has shown non perforated (and often stenosing) ulcer is common but perforation a rarity

The risk of perforation

From what has been said above it is clear that the risk to an ulcer patient that his ulcer will perforate must vary in different countries and possibly at different times

Figures are lacking on which to base an accurate computation but if we use the figures given by Avery Jones and Doll (1951) for the *incidence of ulcer as a whole* and the Glasgow survey figures for the incidence of perforations it is possible to hazard a rough estimate On this basis it would seem that (in this country at the present time) between 0 5 and 1 per cent of male ulcer patients will perforate in any one year Among females the risk is of the order of 0 1 per cent

Types of ulcer liable to perforate

Acute perforation may affect ulcers of the stomach or duodenum the oesophagus the jejunum (stomal ulcer) or Meckel s diverticulum In the duodenum for obvious reasons only an anterior ulcer will perforate acutely into the general peritoneal cavity similarly in the stomach only an ulcer situated anteriorly or extending forwards from the lesser curve A posterior gastric ulcer may perforate at the lesser sac but this is rare for generally adhesions limit the process

Diverse opinions have been expressed as to whether acute or chronic ulcers are more liable to perforation The appearance of a perforated ulcer as seen at operation gives little information on this point for any evidence of chronicity may be obscured by acute inflammatory changes due to the perforation The clinical history is more informative In the Glasgow survey 70 per cent of patients gave a history of indiges tion for more than a year preceding the perforation and nearly 50 per cent gave a history longer than 5 years Admittedly it is possible that the previous symptoms might be due to a different ulcer (for example a chronic symptom producing ulcer on the posterior wall of the duodenum with an acute perforating ulcer anteriorly) but the evidence is all against this view It seems probable therefore that the great majority of perforations affect chronic ulcers

Perforated gastro jejunal ulcer

Free perforation of an anastomotic ulcer into the general peritoneal cavity is less well recognized as a complication of gastro jejunostomy than is penetration into the colon but it is probably no less common In the Glasgow survey among just under 4 000 perforations there were 52 cases of perforated anastomotic ulcer How liable anastomotic ulcers are to perforate could not be determined for the total number of such ulcers (or of gastro jejunostomy) naturally was not known but there seems no doubt that the risk must be much higher than for gastric or duodenal ulcer

Since far more men than women were subjected to gastro jejunostomy and since men are far more liable to anastomotic ulcer it is perhaps not surprising that all the perforations occurred in men

Pathological features

The common appearance of a perforation as though the whole base of the ulcer has given way clearly indicates that the terminal process which ends in perforation is a fulminating one due to sudden devitalization of the ulcer base This cannot be the result of an infective process for bacterial cultures from perforated ulcers are commonly sterile and it seems likely that the explanation is a sudden vascular obliteration with necrosis of the scar tissue in the bed of the ulcer

The pathological effects vary according to the size and site of the perforation A large perforation permits a copious escape of gastric or intestinal contents and wide soiling of the peritoneal cavity whereas a small leak allows little or no fluid and only a small quantity of gas to escape In a gastric perforation if the stomach happens to be distended the leakage is particularly copious and partly digested food may be disposed widely In a duodenal perforation even of large size the amount of fluid escaping is naturally much less It is for this reason that the mortality from duodenal perforations is less than from gastric

Unless the perforation is a large one after the initial leakage little more fluid escapes for a few hours owing to reflex paralysis and consequent immobility of the stomach and duodenum At this stage the perforation may be plugged with omentum and light adhesions form between the perforated viscus and neighbouring organs Under conservative treatment with sedation and suction drainage of the gastric contents the perforation may be sealed off permanently in this way In untreated cases on the other hand more fluid is forced out the adhesions are broken down and the peritoneal cavity is flooded with irritant material At first the fluid is sterile or almost so but in the space of a few hours infection gains access and the initial peritonism is converted into diffuse peritonitis

CLINICAL FEATURES

It is unnecessary to review here all the well known symptoms and signs of perfora tion Instead attention will be focused on particular features of importance particularly those where owing to the changing character of perforated ulcer the classical picture of bygone years must needs be modified

Previous history of ulcer—In the great majority of cases there is a previous history often extending to many years of chronic or periodic dyspepsia and not infrequently the perforation comes as the culmination of a particularly severe attack In a small proportion on the other hand the patient has enjoyed good health and complete eupepsia and the perforation comes as a bolt from the blue In the Glasgow survey 10 per cent of cases were of this pattern

The initial pain—In typical cases the suddenness of the pain at first epigastric but rapidly spreading over the whole abdomen its constant character and continued severity and the accompanying board like rigidity of the abdominal muscles leave little doubt as to the diagnosis Biliary and renal diseases are readily distinguished by the site and radiation of the pain intestinal obstruction by

its colicky nature and by the repeated and increasingly offensive vomit Coronary thrombosis is the main source of diagnostic confusion but may be distinguished by the cardiovascular manifestations and especially the fall in blood pressure Fulminating acute pancreatic necrosis may indeed be almost indistinguishable though in most cases the nausea retching and vomiting point to the true diagnosis On the other hand in the less severe cases which are now more common than formerly the diagnosis is more difficult Here the leak is a minute one or plugged with omentum The initial escape is mainly gaseous or fluid, small in amount Consequently the pain is less severe and may subside after a short time while the abdominal rigidity is more localized and less board like In such cases appendicitis cholecystitis or a simple flare up of the ulcer may cause difficulty

Estimation of liver dullness—This old clinical exercise has surely outlived its usefulness and should be abandoned In former days when gastric perforations predominated and the escape of gas was large and especially if as was usual the patient was seen after several hours delay doubtless the test had a useful place Such cases are now rare, however and when they are seen the diagnosis is usually obvious without special tests In most cases seen at the present day the amount of free gas is inconsiderable

Radiological examination—Free gas in the peritoneal cavity can be displayed with much more certainty by radiological examination According to Olson and Norgore (1946) and Johansson (1947) it is present in rearly 80 per cent of cases

Preferably the patient should be placed in a sitting position so that the air will rise to the subphrenic space but if this is not possible he may be placed in the left lateral position the rays being directed antero posteriorly It must be remembered that occasionally the air is entrapped in adhesions below the liver giving a localized area of translucence which may be mistaken for gas in the bowel

TREATMENT OF PERFORATED PEPTIC ULCER

Conservative treatment—Where operation is performed within a few hours it is often found that the perforation has been sealed off by soft adhesions or plugged by omentum and it is clear that in such cases conservative treatment might be effective

Interest in the conservative treatment of perforation in recent years was aroused by Bedford Turner (1945) and supported by Taylor (1946) who reported a series of 28 cases with 4 deaths (of which 3 were attributed to causes unconnected with the treatment) Visick (1946) later reported 14 cases with 3 deaths Essentially the method adopted (for which reference may be made to Taylor s paper) comprised (1) large doses of opiates (2) evacuation of the stomach contents by hourly aspiration (3) parenteral fluid administration and (4) chemotherapy

Conservative treatment is not suitable where there is a large perforation with a copious escape of fluid and quite apart from the impossibility of recognizing such cases it holds obvious dangers and disadvantages There is the risk of missing such lesions as perforated diverticulum or perforated carcinoma of stomach or bowel or perforated appendix and the disadvantage that conservative treatment demands meticulous attention to detail during several days when a single omission may lead to disaster

These dangers would only be outweighed if the overall death rate could be shown to be greatly reduced but in fact it is at least as high as by operation for which the mortality in some clinics is now less than 5 per cent (Avery Jones Parsons and White 1950) The conclusion seems inescapable that while the conservative method would have been valuable if it had been introduced 20 years ago there is now no place for it except of course in abortive cases where the clinical picture clearly indicates a localized and resolving lesion

OPERATIVE TREATMENT

Pre operative preparation —It has long been recognized that every hour s delay in initiating treatment increases the risk Nevertheless operation should not be undertaken hastily to the exclusion of proper preparation

It is most valuable to empty the stomach thus arresting the spill into the peritoneal cavity obviating the risk of inhaling vomit during anaesthesia facilitating access at operation and improving the post operative course

If the perforation has occurred soon after a meal a full sized tube must be used to evacuate food particles Otherwise a No 16 tube is preferable for it is better tolerated and can be left in position The gastric contents are aspirated either by syringe or preferably by a continuous suction apparatus Lavage should be avoided if possible except for an ounce or so of fluid to clear the tube After operation the tube may be left in position for 24 hours or so to prevent gas distension

Generally no other special preparation is required but in some cases intravenous administration of fluids or blood is indicated

Operative procedure —Twenty years ago the routine practice was to close the perforation and drain the abdomen sometimes by multiple glass or rubber tubes at the site of perforation and suprapubically Now drainage is no longer practised save in exceptional cases seen very late and with gross peritoneal soiling nor is it now considered necessary to evacuate the exudate unless heavily contaminated by food residue The application of antiseptics to peritoneal surfaces has of course long been abandoned and the topical use of sulphonamides also has been given up

At the present time the main subject for debate is the place of various curative procedures such as excision of the ulcer gastro jejunostomy and partial gastrectomy as opposed to simple closure of the perforation

Excision of the ulcer has few advocates in Great Britain Yudin in 1939 reported that in 1 291 perforations he performed gastrectomy on 937 occasions with a mortality of 8 9 per cent which compared very favourably with the results of simple suture at that time but it must be recognized that in this and the many smaller series since reported only the most favourable cases have been selected for the major procedure

It should be recognized that in view of the low mortality of modern operation the old argument that the operation should be limited to life saving procedures no longer holds at any rate for early cases It seems probable furthermore that in skilled hands the mortality from gastrectomy will be little if at all higher in perforations than in interval cases

It follows that if it could be shown that all patients with perforation sooner or later would require gastrectomy there would be a strong argument for the routine performance of this operation (in early cases at skilled hands) at the time of perforation Such an indication is not present however While as will be shown below, the prognosis after simple closure is less satisfactory than previously thought the fact remains that 30 per cent of patients remain completely symptom free for many years and a further 20 per cent have only slight symptoms Thus to perform gastrectomy as a routine at the time of perforation would subject half the patients to an unnecessary hazard In perforated gastric ulcer it is true that the risk of missing a carcinoma must be borne in mind This risk is not inconsiderable for a carcinoma may perforate early and its malignant nature may be masked by inflammatory changes at the site of perforation Doll (1950) has shown that in male patients with gastric perforations an apparently simple ulcer turns out to be malignant in approximately 8 per cent of cases In gastric ulcer especially in males over the age of 40 there seems good reason to advise gastrectomy if the circumstances permit In duodenal ulcer gastrectomy may be justified when continued trouble is expected for example in patients with a long history of severe symptoms or of haemorrhages or a previous perforation it can hardly be justified as a routine

PROGNOSIS

Immediate prognosis

It has long been recognized that the danger to life is related directly to the age of the patient and the length of time allowed to elapse between perforation and operation The danger is greater also in gastric than duodenal ulcer (owing to the greater escape of more heavily infected contents) and is greater in winter than summer (owing to the greater incidence of pulmonary complications)

For many years now owing partly to earlier diagnosis and partly to improved treatment the overall mortality from perforation has been falling In the Glasgow survey for example between 1924 and 1943 the death rate fell from 25 to 14 per cent Since 1943 the risk has been reduced still further by improved preparation and anaesthesia and the use of chemotherapy so that now in some clinics the rate stands at less than 5 per cent (Avery Jones Parsons and White 1950) As these latter workers have shown early deaths from shock peritonitis and such like causes have been eliminated The present day mortality is mainly due to delayed causes such as subphrenic abscess

Long term prognosis

Few aphorisms are so readily disproved as that which says that perforation cures an ulcer Follow up studies reported by many observers show that while most patients enjoy a temporary remission of symptoms a considerable proportion later suffer relapse Probably such improvement as occurs is not due to the perforation *per se* but to the greater care in dieting the prolonged holiday of convalescence and perhaps the altered mental outlook induced as a result of the operation

The precise figures for end results naturally vary in different reports and there may well be true differences due to geographical or racial or other factors but the

general conclusion of other workers is similar to those of the Glasgow survey (Illingworth Scott and Jamieson 1946) which showed that by the end of 5 years 30 per cent remained symptom free while a further 20 per cent suffered only mild or transient symptoms Some 20 per cent suffered a major complication such as haemorrhage a further perforation or symptoms severe enough to necessitate further surgical treatment

REFERENCES

Avery Jones F and Doll R (1951) *Medical Research Council Special Report Series* No 276
— Parsons P J and White B (1950) *B it med J* 1 711
Bager B (1929) *Acta chir scand* 64 *Suppl* 11
Bedford Turner E W (1945) *Brit med J* 1 457
Brinton W (1857) *Ulcer of the Stomach* London Churchill
Brunner F (1903) *Dtsch Z Chir* 61 101
Caird F M and colleagues (1913) *Edin med J* 11 405
Doll R (1950) *B it med J* 1 215
Hurst A F and Stewart M J (1929) *Gastric and Duodenal Ulcer* p 280 London Oxford University Press
Illingworth C F W Scott L D W and Jamieson R A (1944) *Brit med J* 2 617
— — — (1946) *Ibid* 1 787
Jamieson R A (1947) *Ibid* 2 289
Jennings D (1940) *Lancet* 1 395
Johansson O (1947) *Acta chir scand* 95 233
Olson H B and Norgore M (1946) *Ann Surg* 124 479
Rendle Short A (194?) *Lancet* 1 429
Riley I D (194?) *Ibid* 2 485
Spicer C C Stewart D N and Winser D M de R (1944) *Ibid* 1 14
Somervell T H (1942) *B it J Su g* 30 113
Stewart D N and Winser D M de R (194) *Lancet* 1 259
Taylor H (1946) *Ibid* 2 441
Visick A H (1946) *B it med J* 2 941
Wilson A K (1942) *Lancet* 1 335
Yudin S (1939) *J int Chir* 4 219

Section VI

Haematemesis and Melaena

With Special Reference to Bleeding Peptic Ulcer

F Avery Jones

Haematemesis and melaena is an emergency in hospital practice which may cause great anxiety to the patient the relatives and the doctor It is therefore particularly important to be able to make a reasonable assessment of the risk of this common complication of peptic ulcer Recent studies have given much information concerning the prognosis and the value of different forms of management In considering such views on treatment of haematemesis and melaena it is necessary to be able to compare the mortality rates in different series but the intelligent interpretation of the extensive current literature on the subject needs a clear appreciation of the many fallacies relating to them Errors may arise from the method of collection of the figures from their mode of presentation or from intrinsic variations between different series

Mass hospital statistics are liable to appreciable errors unless care has been taken to ensure that an accurate diagnosis has been recorded Individual series remain the most reliable sources of information The personal attention to detail by an interested physician or surgeon and the careful recording of the diagnosis explains the lower mortality in such series compared with contemporary mass hospital statistics The exclusion of fatal cases is now less commonly found in present day series than in the past 20 years Deaths from associated heart failure pyelonephritis acute perforation parotitis may clearly be related to the management of the case and must not be excluded Only two exceptions would seem justifiable first when the patient dies from a clearly unrelated disease (for example tuberculosis) and secondly if an individual having recovered from his haemorrhage undergoes an elective operation and dies his death should not be attributed to the initial bleeding The most important fallacy today in comparing various series relates to the intrinsic variations between series *particularly with regard to age* type of lesion and social status these factors will be carefully discussed in this section

Age distribution is particularly important as the mortality mounts steeply over 60 years and big variations in this age group occur between different contemporary or past series Following the introduction of antibiotics the proportion of those still living to over 70 years is steadily increasing and is clearly reflected in the admissions for haematemesis or melaena This is demonstrated by the experience of the Central Middlesex Hospital where the proportion of admissions over 70 years has risen from 5 to 15 per cent in the past 10 years

It is necessary to know the type of hospital responsible for a published series The mortality is adversely affected by the presence of clinical complications and by the higher proportion of chronic gastric ulcers Both these may be found more frequently among the lower social classes There is a bias on the part of the general practitioner to send the old decrepit ill-cared for ill nourished man to the local regional hospital rather than to a teaching centre Comparison of figures from different countries introduces appreciable errors Geographical variations in the ratio of acute and chronic gastric ulcer and in the gastric-duodenal ratio probably exist The case of admission to hospital under different medical services may also influence the proportion of mild cases treated at home and therefore excluded from hospital statistics

DIFFERENTIAL DIAGNOSIS OF HAEMATEMESIS AND MELAENA

Peptic ulcer is the most important cause of admission for haematemesis and melaena The final diagnosis in the Central Middlesex Hospital series (1940-50) was as follows

Patients with Proved or Probable Peptic Ulcer

	Total
Chronic gastric ulcer group—diagnosed by radiography operation or necropsy including 23 cases of combined chronic gastric ulcer and duodenal ulcer - -	231
Chronic duodenal ulcer group—duodenal ulcer including 23 cases of pyloric ulcer and 67 with previous gastro-enterostomy or partial gastro-enterostomy for duodenal ulcer - - - - - - -	446
Acute lesion group Acute gastritis gastroscopic gastrostaxis (no lesion discovered *post mortem*) Acute gastric ulcer finding observed by gastroscopy usually 3 10 days after admission (90 cases) or *post mortem*	117
Other "radiologically negative" cases - - -	253
Other peptic ulcer cases not classified above Mainly incompleted investigations - - - - -	65
TOTAL	1 112

Other Causes

	Total
Gastric tumours	
Simple - - - - - - - -	4
Malignant - - - - - - - -	28
Portal hypertension - - - - - -	44
Other causes - - - - - - -	33
TOTAL	109
Total peptic ulcer	1 112
GRAND TOTAL	1,221

This series does not include 32 admissions in whom haematemesis and melaena occurred after an acute perforation of a peptic ulcer It was felt that the comparison with such case was fallacious and they needed a *separate study*

In London one may presume that bleeding has arisen from an acute or chronic peptic ulcer unless there is definite evidence to the contrary Difficulty may arise *over cirrhosis of the liver but in practically every case the spleen* is palpable or there are spider naevi present if looked for

Nevertheless one must keep in mind the less common causes of haemorrhage and melaena Oesophageal hiatus hernia should be specifically excluded by the radiologist if there is no other radiological evidence of gastro duodenal disease Hereditary telangectiasia involving the bowel may cause severe bleeding but previous recurrent epistaxis is the usual history in such patients Recurrent un explained haemorrhage may be caused by tumours of the oesophagus stomach or small intestine These include leiomyoma fibroma lipoma haemangioma carcinoma sarcoma or from carcinoma of the pancreas invading the duodenum Such tumours may give a history simulating peptic ulcer (Segal Scott and Watson 1945) Bleeding mav also arise from Meckel s diverticulum diverti culitis of the large bowel or from a solitary peptic ulcer of the small intestine associated with heterotopic gastric mucosa in the ileum (Wilson 1950) Rupture of aneurysms in the alimentary tract may cause serious bleeding these may be syphilitic arteriosclerotic mycotic from bacterial endocarditis and even tuberculosis involving the aorta splenic gastric or hepatic arteries Localized arteriosclerosis of gastric arteries has been described as a cause of haemorrhage (Frank 1946 Engel and Singmaster 1949) Very unusual causes have been recorded for example following exposure to low atmospheric pressure (Schier 1947) or to swallowed leeches (Cameron 1950) General medical conditions such as chronic nephritis thrombocytopoenic purpura and Schonlein Henoch syndrome may cause gastro intestinal bleeding The exact role of acute gastritis *is uncertain* but it does appear that some patients may have very severe and repeated haemorrhage from a diffuse gastritis proved histologically after emer gency partial gastrectomy (Engel and Singmaster 1949) The possibility exists that *some haemorrhages* may be due to aspirin sensitivity Hurst and Lintott (1939) reported that a localized reaction of the gastric mucosa could occur to aspirin and although this has not been confirmed nevertheless *there is a strong clinical* impression that an occasional case is due to aspirin idiosyncrasy

MORTALITY IN RELATION TO SITE AND NATURE OF THE PEPTIC ULCER

There is general agreement that the chronic gastric ulcer carries the highest mortality There is however a statistical fallacy in that acute gastric ulcers may be diagnosed and separated from the chronic group whereas acute duodenal ulcers may cause duodenal deformity and be included with the patients with chronic ulcers In some series it seems likely that radiologically negative cases are presumed to have gastric ulcers and included under this heading

In assessing the prognosis on admission it is of considerable assistance to

decide whether one is dealing with an acute lesion for example an acute gastric ulcer or acute gastritis with which there has been little or no discomfort and no previous history of ulcer demonstrated radiographically or whether there is a chronic ulcer when there has usually been appreciable pain for more than three weeks or a previous history of known ulceration A firm distinction into two groups cannot be made as some patients may have large ulcers and have had little or no pain but nevertheless a positive history of persistent pain or previously known chronic ulcer will clearly indicate a chronic lesion

The mortality of the various main groups at the Central Middlesex Hospital between 1940–50 was as follows

	Number	Died	Per cent
Chronic gastric ulcer	231	44	19
Duodenal ulcer	379	31	8
Post operative group (previous gastro-enterostomy)	67	4	6
Acute lesion group	370	8	2
Portal hypertension	44	12	27
Haemorrhage after admission for acute perforation	3?	12	37

Recurrent bleeding

This provides one of the most important guides to prognosis as may be seen by the following figures which relate to the Central Middlesex Hospital between 1945–50 when a surgical policy in selected cases was in operation

	Cases	Deaths	Per cent
No recurrent bleeding before or after admission	317	4	1 3
Recurrent bleeding before but not after admission	181	3	1 7
Recurrent bleeding after admission only	100	20	20·0
Recurrent bleeding both before and after admission	84	15	17 9

In a previously reported series (Avery Jones 1947) the mortality of brisk recurrent haemorrhage was demonstrated in relation to age and diagnostic groups (*see* Table I)

Meulengracht (1935) has really meant the provision of adequate fluid so desperately needed by an exsanguinated patient and iatrogenic dehydration no longer takes its toll of life Doubtless the more liberal intake of food in the early stages enables the patient to withstand better the hazards of associated complications but this is certainly of less importance than the liberal fluid intake thereby avoiding the severe risks from dehydration The generous use of drip blood transfusions has also greatly improved the care and comfort of the patient The risks of anoxaemia so serious in the elderly have been considerably decreased and has particularly facilitated their nursing care The controversy over the effects of liberal feeding and transfusion can be regarded as finally settled in their favour That they do not increase the frequency of recurrent bleeding but decrease the mortality was clearly shown in the Goulstonian Lecture (Avery Jones 1947) That surgery has a contribution to make to the management of bleeding peptic ulcer is becoming increasingly realized

Surgery for bleeding peptic ulcer

Most clinicians who have had considerable experience in the management of gastric and duodenal haemorrhage would agree that there is scope for surgery in a selected group of admissions but finality has not yet been reached on the best selection of patients or on the best surgical technique to be adopted In no field of medicine or surgery have statistics been more misleading in the past and the figure of most significance is the total mortality of all admissions By the selection of good risk patients it is possible to achieve a very low surgical mortality but with only little improvement to the overall result To make the most impression on the overall mortality one must include the border line risk cases and only then will the individual units come to recognize those cases where the surgical risk is greater than that of continuing medical treatment In 1935 Gordon Taylor demonstrated that massive haemorrhage from chronic ulcers could be treated successfully by emergency operation if carried out promptly At this time surgery had fallen into disrepute as it had been demanded only as a last resort in patients who were anaemic anoxemic and often dehydrated However the introduction of liberal feeding by Meulengracht (1935) and drip transfusion by Marriott and Kekwick (1935) greatly improved the medical care of these patients and although Finsterer claimed a 5 per cent mortality by operating promptly on *all* cases known to have a chronic gastro duodenal ulcer there was considerable feeling in this country that the scope for surgical intervention remained very limited To try to assess the contribution made by *liberal feeding and drip transfusion* Avery Jones (1947) made a study of 400 consecutive admissions of gastro duodenal haemorrhage treated medically with a minimum of surgical intervention and was convinced that in at least 9 *fatal cases* the local and general condition would have allowed surgical intervention This was successfully performed in 7 out of 8 patients during the next 215 admissions There were particular indications for an emergency gastrectomy *in patients over 50 years* with good clinical evidence of chronic ulcer and who had had brisk recurrent haemorrhage after admission Persistence of pain and evidence of arteriosclerosis were further points in favour of operation Since then the experiences at a number of centres in this country have shown that delayed surgery in such patients could be undertaken with excellent results but the exact indications

for selection of cases is not yet agreed The figures published by Tanner (1950) are particularly valuable

TABLE II (Tanner)
PEPTIC ULCER AND GASTRITIS GROUPS
(748 Incidents of bleeding)

		Number of cases	Over 60 years	Operated on	Overall mortality	Average age of patients who died—years
	Period No 1 1941 to 1943—operation avoided as far as possible	193	33	5	10	62
Selective surgical intervention	Period No 2 December 1943 to June 1944—operation earlier always gastrectomy	60	33	15	20	62
	Period No 3 June 1944 to December 1947—operation early simplest to stop bleeding	312	35	11	11	65
	Period No 4 January 1948 to September 1949—Finsterer	183	42	60	7	66

It will be noted that he has purposely avoided putting in the operative mortality figures although they were low because he was not as interested in this as in seeing that the greatest possible number of cases entering hospital with bleeding left the hospital alive It will be seen that his best figures have been obtained in prompt surgery in all patients with proved or probable chronic ulcers

At Birmingham Parsons and Aldridge (1951) have operated on a selected group taking those with the following triple qualification (a) with recurrent brisk bleeding or continuous bleeding after admission for haemorrhage or melaena (b) chronic peptic ulcer the diagnosis being either clinical or supported by previous radiological examination or other investigations in patients and (c) aged 40 years or more

Partial gastrectomy was performed in 50 consecutive cases coming within this group with 7 deaths As the mortality in this group under medical treatment is at least 50 per cent there should have been a material fall in the overall mortality Bohn (1949) has had particularly good results Over three years 135 patients with peptic ulcer bleeding came under his care with a mortality of 7 4 per cent Under the age of 40 years there were no deaths Thirty three patients were operated on with only two deaths He rightly considered his low mortality was due to careful judgment in the selection of case adequate and efficient blood transfusion and early operation Other excellent recent figures have been quoted by Gordon Taylor in his Lettsommian Lectures and an exhaustive review has been compiled by Ivy Grossman and Bachrach (1950)

The Danish experience is well presented by Pederson (1951) and indeed the

recent literature shows that the increasing value of surgery for bleeding ulcer is being appreciated in many countries

Practical aspects of management of haematemesis and melaena

The diagnosis of haematemesis and melaena would not appear to present any difficulties but nevertheless errors can arise Patients with anaemia and with oedema or coronary insufficiency may be admitted with the diagnosis of congestive heart failure angina of effort or coronary thrombosis Disorientation from cerebral anoxia may make it difficult to obtain an adequate history and melaena may not be observed until after admission Pallor may be masked by a dark skin or by artificial light

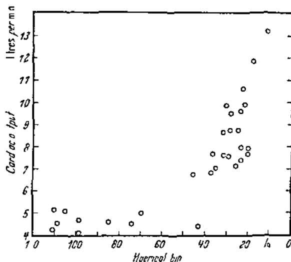


FIG 185 —Graph showing the relation of cardiac output to the degree of anaemia (By courtesy of *Lancet*)

When a diagnosis of haematemesis or melaena is established early reassurance of the patient is essential If necessary this may be augmented by barbiturates or by morphine It is important to realize that morphine may be lethal in patients with severe emphysema and its routine use is not recommended A medical history and examination must be recorded as soon as possible and the severity of the illness must not be used as an excuse for delaying this step which may be essential in deciding subsequent treatment The relatives should also be interviewed and not infrequently they may be able to add useful points to the history The relatives also need reassurance and the opportunity to enrol them for the blood bank must not be missed

Five millilitres of blood should be obtained for initial haemoglobin blood urea and blood grouping tests including Rhesus testing and for serum for direct testing of blood if transfusion is necessary

The nursing staff are instructed to keep in hourly pulse chart and the blood pressure should be recorded if there is increased tachycardia The patient is allowed a semi solid puree diet with 2 hourly feeds of 7 ounces milk feeds if desired the majority will prefer taking food if offered to them Thirst must be entirely prevented by allowing as much $\frac{1}{3}$ normal saline flavoured with fruit juices as desired This should be freely available by the bedside for the first few days

The next decisions relate to blood transfusion and to surgery It is difficult to state precise indications for transfusion It must be remembered that bleeding if recurrent tends to recur at intervals of 12–36 hours and that transfusion is needed not so much for the first bleeding which is seldom fatal but to enable the individual to withstand further bleeding should this occur Giving blood at the rate of one pint in four hours by drip transfusion will restore a reserve but more rapid transfusion may be given if there is evidence of continued bleeding It is essential to prevent the development of anoxaemia for this is particularly liable to lead to restlessness and lack of co operation at all ages and to coma and irreversible shock in the elderly Severe anaemia will itself embarrass the heart by causing a sharp increase in the cardiac output (Fig 185) (Sharpey Schafer 1945)

Again recurrent bleeding in an already anaemic patient invites the small but appalling risk of permanent amaurosis If bleeding has clearly been severe if the patient is still shocked if there is persistent tachycardia and if the haemoglobin has already fallen to 50 per cent transfusion should be begun but the greatest care must be exercised in its performance It is particularly important to make a Rhesus test on women during the reproductive years of life as inability to b ar a live child may follow Rhesus sensitization Scrupulous care must be observed in cross matching and checking of bottles The risk of raising the venous pressure and precipitating acute heart failure must be kept in mind when giving a transfusion to anaemic patients and the jugular venous pressure must be under observation during the transfusion However the risk of acute cardiac failure from careful transfusion is much less than the risk of leaving the patient s haemoglobin below 40 per cent when bleeding may recur

During the days following admission it is de irabl to give an antacid for example Aludrox 2 teaspoonfuls six times a day after feeds and pheno barbitone ½–1 grain 2–3 times a day to maintain mental relaxation The bowels are usually constipated but no action should be taken other than reassuring the patient and giving a simple enema after four days For the patient with duodenal ulcer it is worth considering giving a continuous milk drip through an indwelling rubber tube passed through the nose This has the advantage of enabling aspiration to be performed and further bleeding detected In patients who are desperately ill the stomach may become very distended and aspiration with an oesophageal tube and a stomach pump may improve the general condition If there is anoxemia oxygen should be given either with a tent or a B L B mask

Indication for operation

In arriving at a decision the following points may be considered

(1) Recurrent haemorrhage after admission in a patient middle aged or older known to have a chronic gastric or duodenal ulcer This group has a high mortality under medical treatment and may be regarded as a reasonable indication for surgical treatment particularly a partial gastrectomy

(a) It is not easy to define chronicity Ulcer type pain particularly if severe for 3 weeks is an adequate indication Less pain but with a history of a previous radiological diagnosis of gastric or duodenal ulcer even after a long remission may be accepted

(b) Probably the best surgical contribution to the reduction of mortality comes between the ages of 40 and 70 years The *mortality after recurrent* bleeding under 40 years is much smaller than in the older age range but nevertheless the occasional younger patient may die and operation should not be refused after the second recurrent bleeding in hospital Similarly the upper age range must be elastic A pre senile individual of 65 years leading a vegetative existence *is a more serious hazard than* an alert active man or woman of 80 years

(c) The surgical risk is greatly increased by the presence of complications Particularly serious hazards include a severe degree of emphysema a chronic bronchitis with copious sputum recent coronary infarction calcareous aortic stenosis cerebral vascular disease pyelonephritis particularly associated with nervous disease obesity *broncho pneumonia* heart failure cachexia which may sometimes be associated with very large ulcers in undernourished people and drug addiction

(2) Patients with known chronic ulcer from whose history a partial gastrectomy is clearly indicated and indeed who may be already waiting admission for operation

(a) Whether or not all patients with a known gastric ulcer or duodenal ulcer should be operated on forthwith on admission is as yet not finally decided but this may prove to be justifiable at special centres where surgeons have had a particularly rich experience of emergency surgery

(3) Patients with little or no ulcer dyspepsia and who have recurrent bleeding after admission *These remain a debatable group Operation is certainly justified after* the second or third bleeding particularly in the older age groups It must be *remembered that occasionally a penetrating ulcer may be found in patients* with only slight dyspepsia With increasing experience of local excision of an acute ulcer from within the stomach (Bohn 1949) this group may prove to pay adequate surgical dividends

(4) Patients with simultaneous or consecutive haemorrhage and acute perforation of a peptic ulcer should be considered for an emergency partial gastrectomy Haemorrhage may occur any time in the first 10 days or even later in a small proportion of those admitted with acute perforation These patients do badly and an emergency partial gastrectomy is to be recommended Either double *chronic ulcers or a giant simple* ulcer may be found

(5) Patients with evidence of pyloric stenosis Operation should be considered before further bleeding occurs but a suitable interval should be allowed for *restoring the body fluids and electrolytes*

(6) Patients with previous gastro enterostomy or partial gastrectomy present a special problem Their reputation for being less hazardous than with a known gastric or duodenal ulcer is probably *because many are due to an acute lesion of* the stomach or jejunum causing jejunitis or acute ulceration rather than penetrating ulcers These carry a very low mortality on medical treatment They have usually had little or no recurrent dyspepsia *When there has been* considerable recent pain or when a definite stomach or duodenal crater has been demonstrated *they should be treated as for other chronic ulcer*

ROUTINE INVESTIGATION

The initial haemoglobin may be misleadingly high if haemodilution has not occurred A blood urea of 70–100 milligrams per 100 millilitres is common after brisk haemorrhage but returns to normal in a few days If the blood urea is over 150 milligrams per 100 millilitres the possibility of dehydration chronic nephritis or alkalosis should be considered and extra fluids given An emergency barium meal examination can be given after blood transfusion but this is rarely necessary unless further information is desired by the surgeon A barium meal is unsatisfactory unless the patient can stand and for this reason it is best left until the patient is convalescent 2–3 weeks after the haemorrhage Gastroscopy may be performed at any time If the surgeon wishes for additional evidence of the location of an ulcer before operation it may be performed in the anaesthetic room Gastroscopy a few days after admission is perfectly feasible but apart from clinical research it need not be performed at this time and should never be regarded as an alternative to radiology In cases of suspected cirrhosis hepatis causing haemorrhage brom sulphthalein may give valuable assistance (Zamcheck and others 1950) In their series those with a final diagnosis of cirrhosis all retained 17–60 per cent of the dye at the first examination and a continued high retention was observed with later estimations Normal tests or only a moderately elevated retention which fell rapidly were found in diseases of the liver other than well marked cirrhosis such as fatty liver metastatic carcinoma of the liver and cholangitis A normal retention or one only slightly elevated falling promptly to normal was characteristic of uncomplicated peptic ulcer during convalescence

The stools for occult blood should be determined Should these remain unaccountably positive a barium enema is advisable to exclude a co-existing neoplasm The combination of bleeding duodenal ulcer with carcinoma of the colon is an occasional cause of admission for melaena

ORGANIZATION

The best results can be obtained only by well organized team work between physicians surgeons and pathologists There should be a measure of agreement between the senior staff on the principles of treatment and these should be set out in a schedule available as a general guide for junior medical and nursing staff The duty surgeon should be notified of any patient who comes within a definite group in which surgery may be considered advisable if bleeding occurs The same surgeon may wish to see all admissions but this is seldom practicable unless the hospital is exceptionally well staffed

A 24 hour pathology service for complete blood grouping and testing of blood for transfusion is essential

Arrangements should be made through the Records Department for the accurate coding of the diagnosis and an annual return of the number of admissions and mortality should be available to the medical staff

REFERENCES

Avery Jones F (1947) *Brit med J* 2 441 477
Baker C (1947) *Guy's Hosp Rep* 96 1
Bohn G (1949) *Brit med J* 2 630

Cameron A (1950) *Brit med J* **2** 679
Engel G C and Singmaster L (1949) *Gastroenterology* **12** 146
Frank W (1946) *Ibid* **7** 231
Gordon Taylor G (1946) *Brit J Surg* **33** 336
Hurst A F and Lintott G A M (1939) *Guy s Hosp Rep* **89** 173
Ivy A C Grossman M I and Bachrach W H (1950) *Peptic Ulcer* Philadelphia Blakiston
Lewin D C and Truelove S (1949) *Brit med J* **1** 383
Marriott H L and Kekwick A (1935) *Lancet* **1** 977
Meulengracht E (1935) *Ibid* **2** 1220
Parsons K O and Aldridge L W (1951) *Brit J Surg* **38** 370
Pederson J (1951) *Lancet* **1** 1292
Schier W W (1947) *New Eng J Med* **236** 898
Segal H L Scott W J M and Watson J S (1945) *J Amer med Ass* **129** 116
Sharpey Schafer E P (1945) *Lancet* **2** 296
Tanner N C (1950) *Proc R Soc Med* **43** 147
Wilson E (1950) *Lancet* **2** 855
Zamcheck N Chalmers T C White F W and Davidson C S (1950) *Gastroenterology* **14** 343

CHAPTER 17

CARCINOMA OF THE STOMACH

HERMON TAYLOR

THE remarkable progress that has been made in the general management of surgical cases in recent years has been reflected in the field of gastric cancer by a great increase in the proportion of cases in which the growth can be removed with an equally impressive reduction in operative mortality. Nevertheless the betterment in long term survival has been almost negligible because intervention still takes place too late in the course of the disease. By the time the patient has been moved to seek relief from symptoms and has passed through the diagnostic machine extension or dissemination of the growth has already made it incurable in the bulk of cases. It has become clear that no further progress can be expected until the diagnosis can be established earlier in the disease process. Modern trends of thought are therefore concerned with this aspect of the problem rather than with technicalities. The present position must first be surveyed.

AETIOLOGY

There is some evidence in the Registrar General's Reports that the incidence of gastric cancer is higher in the poorer sections of the community in Great Britain. Jennings has shown that gross statistics suggesting a variable incidence in different countries are fallacious. If comparison is made by age groups and limited to reliable statistics there is no material difference between nations in the incidence of carcinoma of the stomach.

Experimentally it has been found that gross lack of vitamin A induces a papillomatous condition in the fore stomach of rats (Passey, Leese and Knox, 1935). The addition of carcinogenic hydrocarbons to the diet of rats has also produced both polypi and adenocarcinoma of the stomach—an effect which is not altered by liberal allowance of vitamin A (Peacock and Kirby, 1944). The same effect can be produced by subcutaneous injection and Strong (1945) has made the remarkable observation that the malignant tendency so induced in experimental mice tends to be continued in the offspring without further administration of the drug. There appears therefore to be an environmental factor in the genesis of gastric cancer but no clinical significance has so far arisen from these observations.

PRECURSORS OF GASTRIC CANCER

Achlorhydria

The bulk of cases of carcinoma of the stomach occur without any previous history of symptoms to suggest an antecedent change in that organ. In a minority of cases however the growth appears to arise as a complication of a pre-existing condition—

either a peptic ulcer or a diffuse achlorhydric gastritis Comfort and others (1948) at the Mayo Clinic recently investigated a series of 1 347 cases of gastric cancer and found that about 20 per cent of these had had previous symptoms They took as their criterion *patients who had been investigated by test meal at the Clinic more* than two years previously Several cases had been examined on more than one occasion and the average interval between the first investigation and the onset of cancer was 11 years In this way it was possible to study the gastric secretory activity of 277 patients all destined to develop cancer later in life This unique group of cases fell into two parts About a quarter of them had a peptic ulcer with a raised mean gastric acidity The remaining 208 cases had deficient acid secretion being absent altogether in 127 patients In all but five of these the deficiency persisted throughout life from as early as the third decade generally increasing as age advanced so that 69 per cent were completely achlorhydric by the time cancer supervened

Pernicious anaemia

The suggestion that the secretory failure in these cancer prone subjects is due to atrophic gastritis may be linked with the histological studies of Konjetzny and Orator who demonstrated the association of this condition with carcinoma of the stomach Strong support for this idea has recently come from investigation of the frequency of gastric cancer in pernicious anaemia—a disease invariably associated with atrophic gastritis Thus 15 cases of carcinoma of the stomach occurred in a group of 301 patients under treatment for their anaemia in Copenhagen over a period of 21 years (Mosbech and Videbaek 1950) In Minneapolis 36 cases of gastric cancer were found in 293 autopsy records of pernicious anaemia (Kaplan and Rigler 1945) In each of these studies the incidence of carcinoma of the stomach in pernicious anaemia was about 3 times that for a comparable section of the population

It appears therefore that atrophic gastritis may give rise to pernicious anaemia to carcinoma of the stomach or to both of these complications Naturally the frequency with which either occurs singly is much greater than the chance of their *arising together It follows* that carcinoma of the stomach occurs as a complication of atrophic gastritis with a frequency much greater than 3 times that of the general population

If persistent achlorhydria may be taken as an indication of atrophic gastritis it is possible that a careful supervision of achlorhydric subjects might lead to the early detection of some cases of gastric cancer This line of thought is being investigated by Wangensteen *(1947) and his colleagues in Minneapolis* where in 1946 two thousand general out patients over the age of 50 years were considered and test meals were carried out on about half of these Some 301 people were found to be achlorhydric and have since been investigated at intervals radiologically and where possible by gastroscopy Fifteen polypi and one carcinoma were picked out initially The investigation continues

The special group of atrophic gastritis cases *with pernicious anaemia is also* being followed Kaplan Rigler and Fink (1945) have 211 such patients who are radiologically examined at intervals At the time of their first report in 1945 from one to eight radiological examinations had been made on these patients and 7 per

cent of polyps and 8 per cent of carcinomas had been demonstrated There were cases in which both benign tumours and malignant ones were found in the same stomach The malignant change in some polyps was demonstrated Some of the cancers were a considerable size but completely symptomless

Polypi

The frequency of polyp formation is significant because of the tendency of these tumours to become malignant Brun and Pearl (1938) pointed out that polypoid carcinoma is the type most frequently associated with achlorhydria and it seems clear that the pathological sequence is atrophic gastritis with or without pernicious anaemia polyp formation and malignant change in the polyp The degree of malignancy in polypoid carcinoma is generally of a low order and it is unfortunate that this type of growth should be relatively uncommon It is clear however that some cases of cancer are preceded by achlorhydria It remains to be seen how many achlorhydrics develop cancer and the outcome of the experiment at Minneapolis may be of great importance

Peptic ulcer

The demonstration in a tumour of dense scar tissue with histological characters identical with those of chronic peptic ulceration is generally accepted as adequate proof that carcinoma can arise as a complication of benign ulcer Histological criteria must be strict however and it is important not to confuse the deep epithelial heterotopia that occurs in the margin of a chronic ulcer with a malignant change An early misconception about this by Wilson and McCarty (1910) led to estimates of the frequency of neoplastic change in chronic ulcer at first too high then too low Careful work on this question notably by Stewart (1947) now puts the figure at 10 per cent Harnett s (1947) recent figures for London also found malignant change in 10 per cent of ulcers

Opinion on this matter is by no means unanimous Conversely therefore it is interesting to consider the proportion of cancers in which histological signs of previous ulceration can be discovered Stewart found this to be 18 per cent of 281 specimens removed at Leeds over the years 1921–40 Clearly however the original ulcer tissue would be gradually eliminated as the tumour mass grows and sloughs and the chance of detecting it must depend on the stage at which the specimen is examined Clinical diagnosis has tended to be early during the last few years at the London Hospital because of gastroscopic help in doubtful cases and Dr W W Woods has found evidence of peptic ulcer in 11 out of 38 recent gastrectomy specimens It may be therefore that peptic ulcer is responsible for more cases of carcinoma than Stewart s figure suggests

It should be mentioned that a minority of pathologists do not accept the histological signs as evidence of malignant change in an innocent ulcer They postulate instead a primary neoplasm destroyed as it grows by peptic ulceration and scarring (Mallory 1940) This view is more difficult to disprove than to postulate but it does avoid the difficulty of explaining the difference in incidence of ulcer cancer in the prepyloric and mid gastric regions where it is 25 per cent and 5 per cent respectively

Management of peptic ulcer

From the practical standpoint it is clear that all apparently simple ulcers must be suspected of malignancy until the contrary is proved For this reason many surgeons advocate operative treatment for all chronic gastric ulcers on the grounds that the risk is less than that of malignant change and certainly less than that of all com plications put together Ogilvie puts this argument characteristically by the remark that an ulcer in the bucket can never become malignant! However the problem is not so simple as this If the question of malignancy in an ulcer is not determined *before operation what sort of operation shall the surgeon perform*? A simple gastric resection for a malignant lesion would be quite inadequate but must he therefore carry out a widespread extirpation of tissue with its risks and disabilities for a lesion that has a 90 per cent chance of being *innocent*?

The possibility of malignancy in an ulcer is a question that must be decided before any treatment is undertaken Further it must be remembered that delayed neoplastic change may arise later in an ulcer which persists or which recurs after healing Every case of gastric ulcer must therefore be treated to a conclusion Operation must be urged in refractory or recurrent cases but if the ulcer has been seen to heal and shows no tendency to break down the risk of carcinoma is negli gible Walton (1936) found only 8 cases of carcinoma arising in the region of an old ulcer in 1 888 cases treated by conservative operations and presumed to have healed

The only source of error in this scheme of management of gastric ulcer is the *criterion of completion of healing Neither clinical evidence nor radiology is* adequate for all symptoms and most radiological signs disappear early in the healing process The only way to be sure that an ulcer is in fact healed is to observe by gastroscopy its epithelialized scar in the gastric mucosa All ulcer patients presumed to be cured must be examined in this way before they are discharged This rule applies equally to perforated gastric ulcers between 5 per cent and 8 per cent of which are malignant (Doll 1950 Turner 1951) though this fact may not be apparent at operation Successful recovery from the perforation must therefore not be allowed to obscure the question of malignancy until this has been excluded

INVESTIGATION

Indirect methods

Despite the association of achlorhydria with some cases of gastric ulcer at least half the operable tumours are found to occur in a mucosa which looks normal on gastroscopy and is still capable of secreting acid (Taylor 1941a) Engel (1947 found a low acid value in only 30 per cent of operable cases and Walters (1942) states that the incidence of free acid in the stomach is the same in ulcer cancer and benign ulcer Moreover there is evidence that in some cases achlorhydria may develop with the progress of the tumour (Morley 1937) and so indicate not so much the basic diagnosis *but rather a state of advanced disease Clearly therefore* the test meal is unhelpful in the diagnosis of carcinoma of the stomach since achlorhydria is no more than consistent with it while the presence of acid does not disprove it

The test for occult blood in the stools is of some value as a first step in the investigation of a patient presenting with anaemia It is however a fallacy to suppose that carcinoma of the stomach invariably bleeds into the lumen

(Illingworth 1950) and it is important to recognize that a negative result of the test has no significance at all in the search for a growth

Unfortunately the old teaching in these matters dies hard and even now suspicion of cancer tends to be lulled by the discovery of acid in the stomach or the absence of occult blood in the faeces Where carcinoma is in question therefore it is better to omit these tests altogether and to proceed at once to radiological examination and gastroscopy

Radiodiagnosis

A skilled radiologist unhurried can attain a high degree of accuracy in diagnosis In practice however a certain number of errors arise due to misinterpretation of the appearances or failure to detect the tumour (Shanks 1949) Small lesions may escape notice particularly if too much barium is given initially Irregularities at the cardia or fundus may not be discovered unless the technique includes an examination in the inverted position The large flat plastic sheet of growth diffusely infiltrating the anterior or posterior wall of the stomach is liable to be missed or attributed to gastritis or ulcer

At Boston Anglem (1946) found 24 per cent of errors on the first radiological examination in gastric cancer cases 5 per cent being undetected and the remainder misinterpreted mostly as ulcers In London Harnett (1947) found that the radiological accuracy of diagnosis varied with the site of the lesion being 90 per cent for pyloric growths 75 per cent for the cardia and 60 per cent for tumours of the body At Philadelphia Engel (1947) found that 18 per cent of carcinomas of the stomach escaped detection by radiological examination while 34 per cent of positive findings were wrongly interpreted In New York Cooper (1941) reported 70 per cent radiodiagnostic accuracy for the first examination and 90 per cent for the second Presumably the smaller and more operable lesions would be the ones that would be missed and it is important to recognize that radiodiagnosis is fallible An inconsistent radiological report must therefore not be accepted in face of clinical suspicion of gastric cancer

Gastroscopy

Doubtful cases must be examined by the gastroscope which can search the gastric interior independently or can complete the radiological picture with details of configuration and colour In America the original Wolf Schindler flexible gastroscope is still in general use This instrument is flaccid and quite helpless when confronted with an obstruction It takes up an axial position from which it cannot be displaced so that certain parts of the stomach cannot be inspected and lesions may be missed especially if they are causing distortion In carcinoma cases errors and failures with this instrument in American reports amount to about 20 per cent (Engel 1947 Cooper 1941)

These drawbacks were largely removed by the introduction of the Hermon Taylor gastroscope in England in 1939 (Taylor 1941b) In this instrument flexion of the shaft is under the control of the operator who can thereby negotiate obstructions and adjust the position of the objective inside the stomach Lesions can be viewed from a suitable distance and all parts of the stomach can be brought into view unless distortion is extreme The number of errors with this instrument is

therefore reduced to minimal proportions In a series of 67 cases of gastric cancer gastroscoped at the London Hospital there were only 3 instances of failure or misinterpretation

Failure to view the lesion may occur when it is hitched up by extragastric adhesion, usually at the pylorus or lesser curve or when distortion or obstruction at the cardia prevents the safe passage of the instrument Errors of interpretation arise occasionally in the case of a ring carcinoma of the pylorus which may simulate the actual sphincter The mistake most frequently made concerns the question of malignancy in an ulcer The classical ulcerating carcinoma with its thick raised edge is easily recognized and so is the typical peptic ulcer but their distinctive features can be obscured by inflammation In these circumstances it may be quite impossible to detect a neoplastic change in an ulcer and the endoscopist would be unwise to express an opinion until the infection has been reduced by a course of gastric lavage antibiotics and an ulcer regime for 2–3 weeks when a second examination will probably be conclusive An innocent lesion will always improve with treatment whereas malignant tissue will still be lumpy and necrotic and its raised fleshy edge may be more obvious The greatest temptation to the inexperienced is to pronounce malignant the large sloughing ulcer in an elderly patient with a short clinical history The great majority of such lesions turn out to be innocent and respond very rapidly to treatment

Endoscopic biopsy is being developed but it has not yet reached the stage where a specimen can be taken at will from a particular area of stomach wall The technical difficulties are considerable

Where it is a question of detecting small lesions in the stomach gastroscopy must always be carried out before surgical exploration is considered Small malignant tumours still confined to the mucosa are remarkably soft and difficult to feel at operation (Taylor 1947 Moersch and Kirklin 1946 Findley and others 1950) and awkward to view through a gastrotomy incision which may not be suitably placed In these circumstances the surgeon may be in doubt although he holds the stomach in his hand The gastroscopic eye gets a much better view of the gastric interior than that of the surgeon and moreover the examination can be repeated later if necessary

Gastroscopy may also be of value in defining the mucosal limits of larger growths with a view to planning the extent of the radical operation It is of no use in assessing general operability

Endoscopy and radiology of the stomach are complementary examinations Each method has its peculiar limitations but together they make a most reliable diagnostic screen which renders superfluous all other investigations for carcinoma of the stomach except in unusual circumstances

Peritoneoscopy

Peritoneoscopy is disappointing in malignant disease However it is occasionally useful where metastases in the liver or general peritoneum are suspected but not proved To confirm this by operation entails complete preparation for radical removal of the stomach in case the suspicion should prove to be mistaken Peritoneoscopy can be done without preparation the liver and peritoneal surface can be inspected and biopsy may be carried out if necessary Lingering doubts

about the hopeless nature of the case are thereby removed the patient is spared the waste of time and the distress of useless surgery while the hospital conserves its facilities for other work Unfortunately only a limited view of the stomach is possible through the peritoneoscope It has therefore no place in the assessment of local operability which can only be determined by the sense of touch at open operation

Cytological diagnosis

Papanicolaou (1947) recently introduced a new method of diagnosis in the examination of samples of gastric juice for malignant cells Unfortunately it is not always possible to get a good clean specimen of juice particularly in the presence of pyloric obstruction and interpretation of the stained films is difficult At present the method is only 50 per cent positive in cancer cases and 90 per cent negative in non malignant conditions (Pollard and others 1949 Swarts and others 1950) It is therefore not sufficiently reliable in practice but no doubt it will be further developed

TREATMENT

Irradiation

Treatment of carcinoma of the stomach by irradiation is ineffective Fairchild and Shorter (1947) made this clear in a review of various methods of abdominal irradiation They therefore proposed x irradiation of the viscera at open operation in order to give an adequate tumour dose and avoid some of the side effects Of 28 cases of carcinoma of the stomach explored with this in mind 15 of them were irradiated through special sterile applicators In perhaps 8 cases treatment was undertaken with hope of cure but none of the patients lived materially longer than the natural expectation of the disease The best case was a patient with a growth infiltrating the whole stomach but with no involvement of glands who put on weight returned to work and lived two years before dying from widespread metastases This was felt to be encouraging but it is clear that the tumour was of the slow growing type which would be considered operable by modern standards However it is noteworthy that improvement did in fact follow the irradiation and great interest will attend the further work at Mount Vernon Hospital where this experiment is in progress

Modern surgical methods

Surgery remains the only practical method of dealing with tumours of the stomach and new methods have made it safer and available to patients who would formerly have been rejected Before operation measures are taken to promote nutrition by special diet and where plasma protein and haemoglobin levels are low they are restored by transfusion Infection of the mass is reduced by gastric lavage and antibiotics and instruction in breathing and leg exercises is given to combat post operative embarrassment of the lungs and circulation

Post operative care has undergone a similar development Continuous gastric aspiration prevents tension on suture lines bronchial aspiration aborts pulmonary collapse intravenous control of electrolyte and protein metabolism supports the

circulation and early ambulation or anti coagulants forestall or cut short thrombotic complications Greatest of them all is penicillin and the newer anti biotics which ensure the sterility of wounds effusions urinary tract areas of pulmonary collapse and other conditions which formerly threatened the patient s recovery Modern methods of anaesthesia now provide absolute relaxation of the abdomen without intoxicating the patient and the surgeon has ample time to *carry out his technique*

Design for operation

Until recently the dissection involved in a gastrectomy for cancer perforce differed little from the operation for ulcer notwithstanding the possibilities of lymphatic spread beyond this limited field With the removal of the restrictions formerly set by the tolerance of the patient the surgeon may now design the operation as a block dissection similar in principle to other radical excisions for carcinoma The separation therefore follows the foetal plane of adhesion between the great omentum and the transverse colon along the lymphatic watershed between coeliac and superior mesenteric systems On the left the spleen is mobilized and on the right the glands round the right gastric and gastro epiploic vascular roots are dissected towards the stomach Intermediately the peritoneum of the lesser sac which may contain malignant implants is lifted up with the specimen The left gastric vessels are divided at their origin the glands round the coeliac axis are stripped up with them and the lymphatic tissue round the cardia is swept down wards from the diaphragm The mass that is removed therefore consists of the whole stomach except the fundus both omenta the spleen and all the regional glands If the growth has become adherent to the left lobe of the liver the body of the pancreas or the colon the surgeon has no hesitation in removing any of these structures with the specimen the loss of which is rarely followed by any derangement of digestion or metabolism The abdomino thoracic operation for growths involving the cardia will not be discussed here

Widespread enlargement of glands does not in itself contra indicate a radical dissection because this is commonly inflammatory in nature due to infection of the growth Rapid histology carried out near the operating theatre is a facility which may be of great help to the surgeon For example if distant glands are clear he is justified in subjecting the patient to a radical operation in order to affect a cure but if they are involved in widespread dissemination a more conservative operation is called for concentrating on rapid immediate convalescence

Duodenal infiltration

The statement by Rokitansky nearly a century ago that cancer of the stomach was limited absolutely by the pyloric ring has apparently been passed too readily from teacher to student since then In 1936 Castleman first demonstrated malignant cells infiltrating the duodenum up to 2 centimetres in 10 per cent of all cases Zinninger and Collins (1949) found that where the primary growth lay within 5 centimetres of the pylorus the duodenal wall was infiltrated in 30 per cent of cases Fodden (1948) finally showed that the obstacle to the spread of malignant cells was Brunner s layer of glands which take origin from the distal side of the pylorus and shield the duodenal mucosa from invasion No such protection exists in the

seromuscular coats which Fodden found to be infiltrated in 16 out of 50 cases of gastric cancer The infiltration was always farthest along the *superior surface of th duodenum* in continuity with the lymphatics of the lesser curve of the stomach though it rarely extended more than one inch from the pylorus From these studies it is clear that the operation for carcinoma of the stomach should include removal of at least one inch of duodenum

Total or subtotal gastrectomy

Extension of the growth towards the cardia raises questions of a different character In 1934 Verbrugghen showed that in the case of macroscopically well defined lesions lymphatic permeation in the stomach wall rarely extended beyond 35 millimetres from the edge of the tumour This observation has an important bearing on the extent of proximal resection of the stomach and particularly in the choice between total and partial gastrectomy Until recently this choice has been determined by the great difference in risk between the two operations Pack and McNeer (1943) found the average mortality for total gastrectomy was 38 per cent in cases collected from the lit rature However it must be remembered that this figure applies to growths e tending high in the stomach where there is no alternative to removal of the whole viscus if all the malignant tissue is to be cleared For pyloric growths with normal tissue at the cardia the risk would be much less Lefevre and Lortat (1950) distinguish carefully between *Gastrectomie Totale Obligatoire* and *Gastrectomie Totale de Principe* for distal cancer where partial gastrectomy would be a po sible alternative Lahey and Marshall (1950) have shown that there is now little difference between the risk of partial gastrectomy and elective total gastrectomy—their recent mortality being 9 per cent in each case Longmire (1947) who has had 2 deaths in 20 total gastrectomies for distal growths suggests this operation as a routine procedure The argument for this policy rests upon the demonstration of malignant cells near the proximal edge of part al gastrectomy specimens and upon the development of recurrent growth in the gastric stump in follow through cases At the Lahey Clinic the latter was demon strated in 20 per cent of autopsies for recurrent carcinoma In Paris Lefevre (1947) was able to perform a secondary total gastrectomy for recurrence in the gastric stump in 3 patients out of 15 such cases He made the observation that the recurrence in these cases was associated with the gastric suture line either at the junction with the jejunum or at the line of closure of the stomach above this It would seem therefore that the recurrence arose from malignant tissue left in the wall of the stump of the stomach and not in some outlying lymph gland The problem however is not limited to considerations of the risks of operation and recurrence After removal of the whole stomach a curious inanition is apt to develop which may be fatal This tendency appears to be distinct from iron-deficiency anaemia and derangement of fat digestion which are generally controllable West (1949) describes a patient who died from progressive weakness and wasting some months after total gastrectomy despite the administration of a full diet containing adequate calories and all known essential food substances Two of Longmire s cases died from inanition and Smith (1947) found 7 deaths from this cause in a review of the results of 43 total gastrectomies It is important to stress that the majority of patients do in fact lead a fairly contented life after total gastrectomy and some

return to work The disability and risk must therefore be accepted in the case of diffusely infiltrating carcinoma of the stomach but are too high a price to pay for a doubtful advantage when the growth is well defined and clear of the cardia

RESULTS OF SURGERY

Immediate results

Correct assessment of surgical results can only be made *in relation to the total* number of cases Unfortunately reports in this country tend to refer only to the operative results of individual surgeons without relation to the whole The report of the British Empire Cancer Campaign on Carcinoma of the Stomach which records all cases admitted to the major voluntary and municipal hospitals of London between January 1938 and September 1939 is therefore of great import ance In this series the growth was removed in 17 per cent of a total of 1 405 cases with an operative mortality of 33 per cent

In the United States where the bulk of hospital operations are performed by the resident staff reports are more frequently on a hospital scale The trend of results can therefore best be estimated *from American sources Excellent accounts come* from the large private clinics At the Mayo Clinic (Walters and others 1942) nearly 11 000 patients with gastric cancer were dealt with in the 30 years from 1907–38 and the growth was removed in 25 per cent of cases with a death rate of 17 per cent The disparity between these results and those in London is partly due to the lower average age and generally less advanced disease seen at the Mayo Clinic than in the General Hospitals of London At the more comparable Bellevue Hospital in New York where all sorts of patients are admitted the resectability rate up to 1945 was 14 per cent with a mortality of 62 per cent (Abrahamson and Hinton 1947)

Since these figures were produced the immediate results of surgery have improved remarkably In Massachusetts General Hospital in 1948 75 per cent of cases were explored 50 per cent of growths were removed and the mortality was reduced to 4 per cent for subtotal gastrectomy and to 30 per cent for total gastrectomy (Welch and Allen 1948) In Minneapolis the combined efforts of twenty surgeons on the staffs of the University Hospitals raised the resectability rate from 28 per cent to 80 per cent and lowered the mortality from 25 per cent to 5 per cent in the period 1936–45 (State and others 1947)

Five year cures

The effect of these figures on the long term results of treatment has been dis appointingly small The latter are best expressed as five year survivals because a patient who has lived that length of time after an operation has the same expecta tion of life as a person of corresponding age in the general population Berkson made this important observation from *his analysis of the large figures at the* Mayo Clinic already mentioned He found it to be true also for the various types and grades of tumour It is therefore fair to apply the term five year cures in relation *to this disease* and convenient to use the proportion of these in a given series as a measure of the late results of treatment

At the Massachusetts General Hospital five year cures for the period 1931–36

constituted 5 per cent of all cases A decade later it was no more than 7 per cent notwithstanding all the technical advances that had been made in the interval In Minneapolis the five year survival rate for the period 1936–45 was also 7 per cent of all cases Actually since the normal expectation of life in the cancer age group is less than 100 per cent the results of treatment are about one tenth better than these figures imply Even so they are desperate

PROGNOSIS

Neither the macroscopic nor the microscopic characters of the primary tumour provide any foundation on which to forecast or anticipate the results of treatment especially in individual cases (Steiner and others 1948 Moore and others 1948) The most that can be said for pre operative typing and grading of tumours is that the clearly defined lesions tend to do better than the diffusely infiltrating masses The extent of lymph node involvement determined by examination of the whole excised specimen is a more reliable guide Where the glands are clear the five year survival rate lies between 50 and 70 per cent Where they are involved the chance of cure after radical excision is reduced to between 10 and 15 per cent In Minneapolis Wangensteen is investigating the possibilities of a second laparotomy six months after the first operation to look for glandular metastases which may have become evident in the interval His present impression however is that the procedure is more promising after colectomy than after gastrectomy

DELAY IN DIAGNOSIS

The poor chance of ultimate cure that still obtains notwithstanding the great improvement in operative management is the dominating fact of the present position of carcinoma of the stomach The problem of delay in treatment after symptoms have arisen is therefore a matter of grave importance This may be divided into three periods according to responsibility—the period of initial symptoms before medical consultation the delay in reference to hospital after the complaint and delay in hospital itself The latter has already been discussed in considering the fallibility of methods of investigation It is enough to add that in Boston Anglem found that reliance on a single radiological examination led to an average of 14 months delay in cases where the report was in error This is the simplest of the three problems calling in general for a better appreciation of the reliability of diagnostic aids and in particular for the more frequent combination of radiological examination and gastroscopy in doubtful cases

Delay in reference to hospital by the general practitioner is variously reported as between 3 months and 17 months (Anglem 1946 Harnett 1947) It is partly the result of the old teaching that gastric cancer is characterized by abdominal pain vomiting anorexia wasting and a palpable lump in the abdomen In fact a palpable mass is uncommon and none of the symptoms mentioned may be present at the operable stage There may be no abdominal symptoms at all or they may seem to imply a disturbance of function of the colon rather than the stomach Alternatively the dyspepsia which occurs in half the cases may simulate ulcer very closely Acute bleeding is rare and only obstruction at the pylorus or cardia presents

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recent conception in the United States therefore is a system of Cancer Detection Clinics which healthy people over 45 years would attend much as they arrange a periodical inspection by their dentist At the Clinic cancer would be the sole object of scrutiny question examination and investigation Diagnosis would not wait upon illness and might thereby be made at an early stage The idea will doubtless encounter spontaneous opposition in conservative minds but it is worthwhile to consider what might be achieved If metastasization in a growth is a question of the time factor—a matter that is by no means established—abolishing a delay of 12 months might reduce by one third or one half the period during which the un suspected growth is free to disseminate If this were so the late results of operation might improve immeasurably Translated into fractions of the 15 000 deaths that occur annually from g stric cancer in Great Britain together with similar figures for the colon rectum breast and uterus the prize of success would b high indeed In America free medical enterprise and an informed public opinion has resulted in experimental pilot plants in Cancer Detection Clinics being set up The problem is no longer a purely clinical one and the results of this great experiment in social medicine will be awaited with eagerness on this side of the Atlantic

REFERFNCES

Abrahamson R H and Hinton J W (1947) *Surg Gynec Obstet* 84 481
Alvarez W C (1931) *J Amer med Assoc* 97 77
Anglem T J (1946) *New Engl J Med* 235 32?
Brun H and Pearl F (1938) *Amer J Surg* 40 51
Castleman B (1936) *Ann Su g* 103 348
Comfort M W Kelsey M P and Berkson J (1948) *Proc Mayo Clin* 23 135
Cooper W A (1941) *J nat Canc Inst* 2 85
Doll R (1950) *Brit med J* 1 215
Engel G C (1947) *J Amer med Assoc* 135 687
Fairchild G C and Shorter A (1947) *Brit med J* 2 243
Findley J W Jun Kirsner J B and Palmer W L (1950) *Gastroenterolo y* 14 502
Fodden J H (1948) *Brit J Canc* 2 239
Hansard House of Commons (1950) 14 D c
Harnett W L (1947) *B it J Surg* 34 379
Illingworth C F W (1950) *Brit med J* 2 262
Kaplan H S and Rigler L G (1945) *Amer J med Sci* 209 339
— — and Fink D (1945) *J Amer med Assoc* 128 4?6
Lahey F H and Marshall S F (1950) *Ann Surg* 132 540
Lefèvre H (1947) *Rev Chir Paris* 85 257
— and Lortat J (1950) 53 *Congr Fr de Chi Paris*
Longmire W I Jun (1947) *Surg Gynec Obstet* 84 21
Mallory T B (1940) *Arch Path* 30 348
Moersch H J and Kirklin B R (1946) *Gastroenterology* 7 285
Moore G E State D Hebble R and Treloar A E (1948) *Surg Gynec Obstet* 87 513
Morley J (1937) *Brit m d J* 2 950
Mosbech J and Videback A (1950) *Ibid* 2 390
Pack G T and McNeer G (1943) *Int Abst Surg* 77 265
Papan olaou O N and Cooper W A (1947) *J nat Ca c Inst* 7 357
Passey R D Leese A and Knox J C (1935) *J Path Bact* 40 198
Peacock P R and Kirby A H M (1944) *Canc Res* 4 88
Pollard H M Bryant H C Block M and Hall W C (1949) *J Amer med Asso* 139 71
Shanks S (1949) *Proc R Soc Med* 40 111 117
Smith F H (1947) *Su g Gynec Obstet* 84 40?

symptoms of any urgency Teaching should emphasize that there is no typical picture of gastric cancer but that the symptoms are insidious and equivocal while clinical signs may be lacking

Practitioners must be on the watch for the diffident person consulting a doctor for the first time in his life about some new though persistent symptom Such a case must be investigated and if necessary treatment should be withheld until the possibility of cancer is excluded Unfortunately facilities for investigations are too often lacking in general practice Reference to hospital is the only means and the doctor hesitates to send the case away for reasons which may be psychological as well as material Temporizing treatment often results in relief of symptoms and the opportunity of early diagnosis may be lost with fatal results to the patient More radiological facilities are required if all suggestive cases are to be examined and they must be placed within easier reach of the general practitioner (Taylor 1948)

EARLY DIAGNOSIS AND THE PUBLIC

A more difficult problem is the delay on the part of the public in recognizing the need to seek advice for their symptoms This period varies between 3 and 9 months (Engel 1947 Anglem 1946 Harnett 1947 Cooper 1941) according to different investigators People dislike making a fuss and the early symptoms of gastric cancer are often amenable to self medication and easily ascribed to irrelevant circumstances There is however no case to be made for the official discouragement of public education in the simple facts of early cancer which obtains in Great Britain (*Hansard* 1950) If intelligent people are to bring their early symptoms to the doctor without annoying him with trivialities they must surely know what to look out for! The fear is expressed that such knowledge would induce a widespread cancer neurosis among the people but it would be more true to say that the fear of cancer in ordinary people lurks in the dark corners of the mind and not in the light of knowledge Unfortunately cancer education is not the whole of the matter Alvarez (1931) at the Mayo Clinic found that medical men themselves delayed almost as long as their patients before seeking advice for their own symptoms

It is therefore relevant to compare the duration of delay in diagnosis with the life span of the growth Naturally this varies from the fulminating type that metastasizes in lungs and bones at an early stage to the tumour that remains local for years Both these types are uncommon however and it is likely that the life of most gastric cancers is ordinarily between 2-3 years Wangensteen inferred this from the observation that after incomplete removal of a tumour in the stomach wall 18 months usually elapsed before signs of recurrent growth appeared Welch and Allen add that since gastric cancer is a rare incidental finding among general autopsies compared with prostatic cancer it must run a relatively short course If these estimates are correct it appears that delay in diagnosis at present covers about one third of the life of the tumour

CANCER DETECTION CLINICS

It is apparent that the main obstacles to early diagnosis derive largely from human failings On the one hand the patient resists the suggestion of illness and on the other the doctor for a variety of reasons may not suspect malignant disease A

CHAPTER 18

AFTER GASTRECTOMY

W M CAPPER

THE DECISION to remove the greater part of the stomach to relieve benign ulceration is a mutilating procedure and one which must obviously be thoroughly scrutinized not only with regard to its immediate but also to its long term effects on general physiology The operation has been practised for many years and has now become firmly established It can be categorically stated therefore that it is unlikely to give rise to any undesirable side effects in the vast majority of cases The patients are well pleased with their operation and are delighted to be finished with their persistent indigestion restricted diet and ulcer pain The operation should no be regarded as successful if restrictions have to continue afterwards In a routine follow up many will be found who 10 years after the operation have almost for gotten that they ever had any indigestion There are however certain sequelae of the operation which may arise and cause a degree of inconvenience sufficient to give the patient anxiety and in a few cases sufficient to interfere with his work It is to the consideration of these comparatively rare cases that this study is confined

The problem in its most simple form is plainly a question of how far the stomach is an essential organ Obviously the removal of the stomach will result in the loss of a capacious and efficient re ervoir and mixer of food Peptic activity will also be considerably reduced but this should be adequately covered by the far more efficient proteolytic enzymes readily available in the pancreatic juices It must be borne in mind however that where a Polya operation is done the biliary and pancreatic flow is side tracked so there may not be such efficient mixing of the food with these important juices The diminution in production of hydrochloric acid is probably more serious though it is clear that a large number of patients with an intact stomach are free from any serious side-effects even in the presence of a long standing achlorhydria Many investigators have shown however that the absence of adequate secretion of hydrochloric acid causes a failure in the full utilization of ingested iron so that the haemoglobin level may eventually fall It must also be remembered that hydrochloric acid is a potent sterilizer of the ingested food before it is passed on to the delicate absorbing mechanisms of the mid gut which nature is at pains to protect in this way A further gastric function which must be considered is the production of Castle s intrinsic factor which is essential to the maintenance of normal blood formation With these gastric functions in mind therefore it is to be expected that certain upsets in physiology will follow gastrectomy unfortunately in addition to what may be anticipated other side-effects sometimes occur which may considerably distress the patients The most important of these has been given the name of the Dumping Syndrome

State D Moore G E and Wangensteen O H (1947) *J Amer med Assoc* **135** 262
Steiner P E Maimon S N Palmer W L and Kirsner J B (1948) *Amer J Path* **24** 947
Stewart M J (1947) *Brit J Radiol* **20** 505
Strong L C (1945) *J nat Canc Inst* **5** 339
Swarts J M Ragius A B Bernstein A and Meyer J (1950) *Gastroenterology* **14** 265
Taylor H (1941a) *Lancet* **1** 131
— (1941b) *Ibid* **2** 276
— (1947) *Brit J Radiol* **20** 507
— (1948) *Lancet* **1** 581
Turner F P (1951) *Surg Gynec Obstet* **92** 281
Verbrugghen A (1934) *Arch Surg* **28** 566
Walters W (1942) *Ann Surg* **115** 521
— Gray H K and Priestley J T (1942) *Carcinoma of the Stomach* Philadelphia Saunders
Walton J (1936) *Lancet* **1** 1101
Wangensteen O H (1947) *J Amer med Assoc* **134** 1161
Welch C E and Allen A (1948) *New Engl J Med* **238**, 583
West J P (1949) *Ann Surg* **129** 373
Wilson L B and McCarty W C (1910) *Amer J med Sci* **138** 846
Zinninger M M and Collins W T (1949) *Ann Surg* **130** 557

(a) *Primary Addisonian anaemia*

It might be expected that the removal of the stomach would interfere very considerably with the production of the intrinsic factor of Castle thus the maturation of blood cells would be adversely affected and a primary Addisonian anaemia gradually develop Ever since Castle in his original work in 1929 showed the importance of this aspect of gastric function considerable attention has been given to the matter Indeed after the publication of his findings some surgeons recommended routine liver feeding following operation Fortunately it may be stated unequivocally that pernicious anaemia following gastrectomy is not only unusual but distinctly rare Lake (1937) found no case in 300 gastrectomies and Ogilvie (1935) none in 140 I have found one case in 372 follow ups Furthermore Sturgis and Goldheimer (1939) were unable to find any cases of macrocytic anaemia in 271 patients who were very carefully followed up after major gastric surgery This may be due to the fact that some of the intrinsic factor is secreted by the fundus of the stomach even though this occurs to a much greater degree in the body This seems to be compensated however by the fact that the intrinsic factor is most active at *p*H 7 (Castle and others 1937) Whatever may be the reason in practice anaemia appears to be no more common after gastrectomy than before

(b) *Secondary anaemia*

Iron is absorbed mainly from the least alkaline part of the gastro intestinal tract (Cartwright 1947) that is the first part of the duodenum Obviously if the maximum absorption is to occur hydrochloric acid is necessary It may be expected therefore that an operation which designedly reduces the hydrochloric acid to minimum proportions would give rise to an iron deficiency anaemia Watson (1947) in an admirable review of the condition concluded that as many as 10 per cent may develop this Wells and Welbourn (1951) using Whitby and Britton s minimum haemoglobin standards state that there is an iron-deficiency anaemia in 20 per cent of men and 30 per cent of women at periods varying from 1 to 4 years after subtotal gastrectomy Muir (1949) found moderate anaemia in 15 out of 22 gastrectomies in women whereas it only occurred in 2 out of 102 gastrectomies in men It is definitely more common after operation for gastric ulcer as might be expected from the lower acid values in that disease as compared with duodenal ulcers A further factor which may be significant is that Morley (1928) found that secondary anaemia was less frequent after the Billroth I than after the Polya operation My impression is that this view is correct

The onset of the anaemia is usually insidious and slowly progressive It is almost always microcytic in type and the response to iron is excellent Hartfall (1934) in an assessment of the condition found that the patients who had a secondary anaemia following operation were precisely those who had remained abstemious in their diet following operation so that they were eating food which was deficient in haematinic principles It is important in this regard to insist that the patients should take red meat protein eggs and green vegetables It is furthermore essential that the blood loss which may have occurred before or at operation is completely replaced before discharge from hospital otherwise such anaemia may steadily increase

It is found in practice that there are other factors such as failure to regain normal weight loss of energy and diarrhoea which may also be an outcome of the operation Many of these side effects have not yet been entirely worked out nor are the problems attached to the mechanics of this operation completely solved but sufficient experience has been gained in many centres to be able to make a general statement with regard to most of them and indeed to be able to set out measures which should in some degree at any rate prevent their occurrence

Before the consideration of these rare—but unfortunately possible—sequelae it may be advisable to outline suggestions as to the immediate post operative care of the patient The first of these is an early return to a normal full diet It should be possible for the patient to be *taking full meals by the time he leaves* hospital in 10 or 14 days after the operation He should be told to chew thoroughly and to avoid swallowing large lumps of food In this way the mixing of food normally done by the stomach will be assisted and for this purpose a good set of teeth is important He may find that there are still one or two items which he must avoid in his dietary as they may cause heartburn or indigestion and the patient *himself will be the best judge of these In some cases these will be found to consist* of pickles sauces twice cooked meats spices spirits or fried foods such things *indeed as may cause indigestion in persons of normal constitution It is important* to tell him that his stomach is smaller since the operation and that he may expect to experience some fullness after meals but that this will tend to pass off after a year or so Repeated barium meals show that the gastric remnant stretches con siderably over the years Contributive psychological factors are also important and he must be explicitly told that his ulcer has been completely dealt with together with the factors which caused it and that he need not expect any further in digestion provided he follows a reasonable diet and way of life The haemoglobin *should be estimated in all cases before discharge and should be at least 95 per cent* (Haldane) It is wise to have a fractional test meal carried out for purposes of record in case later trouble develops He should not be allowed to remain off work for too long or he will soon regard himself as an invalid and the operation as too much of a major procedure He should be back at ordinary work by 8 weeks and should be able to manage heavy work in 3 months It is customary to tell every patient to have a course of ferrous sulphate and extra vitamin B in the form of Bemax Marmite or yeast for a month every year for the rest of his life and to get him to report *for a follow up every 3 months for a year and every year* for the next 5 years So many of the e cases with post gastrectomy syndromes have in the past been regarded as neurotic and their symptoms minimized or disregarded that it is found worthwhile to follow them up in this way *Such symptoms are* often very real and failure to understand and at least explain their nature further mystifies the patient and may contribute to a dissatisfied outlook on the operation

Among the conditions which must be watched for in such a scheme of follow up are those arising from (1) disturbances of nutrition (2) recurrence of ulceration and (3) *the specific post gastrectomy syndromes*

(1) Disturbances of nutrition

(a) Primary Addisonian anaemia (b) *secondary anaemia* (c) *failure to gain* weight (d) vitamin lack and (e) lack of energy

part of the intestinal tract for their absorption Muir (1949) how ver found two male patients with mild scorbutic symptoms which rapidly responded to vitamin C These cases had apparently been on a vitamin C deficient diet previous to operation In addition to four cases of vitamin B_2 deficiency Adlersb rg and Hammerschlag (1947) describe one case of mild vitamin A deficiency which was associated with a post gastrectomy syndrome Wells and Welbourn (1951) have made some very important observations in this connection They report a syndrome consisting of a sensation of pins and needles in the extremities muscle cramps fatigue and loss of energy in 10 per cent of cases between 1 and 4 years after operation which responded to 3 milligrams of aneurin daily by mouth over 6 weeks Some observers have described comparatively rare cases of peripheral neuritis with oedema and another reports two cases of Wernicke s encephalopathy Such cases usually respond rapidly to aneurin

Angular stomatitis and glossitis from ariboflavinosis may also be seen though usually it does not make its appearance until 5 years or more after operation It is therefore wise to question the patients directly for evidence of flaking of the tongue or soreness at the corners of the mouth Evidence of deficiency in nicotinic acid is very rare though it has been described (Wells and Welbourn)

In view of the likelihood of the comparatively insidious development of such deficiency diseases it is usual practice to instruct the patient to put himself on a course of extra vitamin B feeding for one month every year for the rest of his life He is usually advised to take Marmite yeast and Bemax and in some cases to have aneurin 15 milligrams and riboflavine 3 milligrams twice a day during this month In this way it is hoped to avoid such deficiencies occurring

(e) *Lack of energy*

A further symptom which may or may not be associated with avitaminosis is lack of energy A few patients complain bitterly of this and so far no evidence as to its cause can be seen The fatigue comes on at the end of the day and is not associated with the early post gastrectomy syndrome which may produce brief periods of lassitude Wells and Welbourn have described a similar condition and state that it is sometimes relieved by aneurin

(2) Recurrence of ulceration

This is a possibility which must always be borne in mind where there is recurrence of pain following gastrectomy and especially where the operation has been done in a male with duodenal ulceration in the pre ence of high acid values The incidence in such cases depends largely on the type of operation carried out In one series of gastro jejunostomies for instance (Wright 1934) stomal ulcera tion was found to occur in 6 per cent Before this operation is undertaken therefore the degree of pyloric stenosis the acid values in the fractional test meal and the mucosa as seen on gastroscopy must be carefully considered Now that gastrectomy is done more frequently in comparatively young duodenal ulcer patients with high acid values secondary jejunal ulceration is becoming more common These intense obsessional young men need careful consideration before operation is undertaken for their relief and this should probably always be accompanied by a vagotomy Even in spite of all such precautions however a

It is not difficult to find records of a severe secondary anaemia occurring in cases as long as 15 years after gastrectomy It is therefore usual practice in all cases to advise a course of ferrous salts for a month every year following operation for the rest of the patient's life

(c) *Failure to gain weight*

There are a few patients who complain that following the operation they are unable to regain their normal weight Sarah Jordan (1941) in her series found as many as 29 per cent had difficulty in maintaining their normal weight Adlersberg and Hammerschlag (1949) found that there was an average loss of 10 lb as long as 7 years after operation A few patients are seriously perturbed by this effect and tend to exaggerate the factor and so regard the operation as a failure Muir (1949) regards it as an important side effect, and found that out of 86 gastrectomies, less than 10 per cent had gained weight and 40 per cent had lost 1 stone or more In investigating these cases he found that 5 out of 7 patients who were under weight without other obvious reason had a definite steatorrhoea These findings concur with those of Wollager (1949) who in a carefully controlled experiment showed that all such cases excrete an abnormal percentage of fat whether they are on a high or a low fat intake Moreover most of them have an excessive nitrogen loss also even in the absence of clinical symptoms The cause of loss of weight is probably rapid emptying of the gastric remnant and hurry of the food through the alimentary tube associated with a failure of thorough mixing of the food with pancreatic juices and the bile Wells and Welbourn (1951) have slowed the rate of passage through the small bowel in these cases with hexamethonium bromide and been able to increase the fat absorption from 74 to 89 per cent and thus caused the patient to put on one stone in weight in a month It can be shown that the afferent loop in certain cases becomes loaded with bile and pancreatic juices which only empties efficiently at infrequent intervals It may be that these cases excrete excess fat during these retention periods Some authorities treat these cases with six small meals a day and double the fat intake One further important aetiological factor in this connection is that cases with the early post gastrectomy syndrome are afraid to eat large amounts as it brings on their symptoms These cases nearly all suffer markedly from loss of weight Whether they have steatorrhoea as well has not as far as I know been accurately determined though the impression is that they have

In view of these findings gastrectomy must not be lightly advised if a patient with an ulcer has phthisis where post operative loss of weight may have a serious outcome Apart from such cases and where loss of energy accompanies it patients can be reassured on the matter It is the practice in cases with real anxiety to tell them that many people are too heavy and that the loss of weight will actually benefit them

(d) *Vitamin lack*

It is likely that where there is intestinal hurry lack of hydrochloric acid and the presence of bacteria in the jejunum there will be a corresponding deficiency in the absorption of vitamins Such deficiencies are generally confined to the vitamin B group which is not entirely unexpected seeing that aneurin and riboflavine are unstable in alkaline solution and depend upon the acidity of the upper

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stomal ulcer may appear as we have seen recently where a woman aged 73 developed ulceration 9 months after gastro jejunostomy for a duodenal ulcer It is well recognized that gastrectomy with entero anastomoses or conservation of the pyloric antrum will lead to jejunal ulceration in a high percentage of cases and for this reason such procedures have been abandoned in Great Britain The figures given for stomal ulceration following subtotal Polya operations is about 2 per cent of cases Visick (1948) however has reduced this figure to an almost negligible amount by doing a much higher operation Such ulcers are usually situated on the first 5 centimetres of the afferent jejunal loop though they may be present on the gastric side of the stoma The patients complain of intense pain which is often continuous though it may be relieved by vomiting They usually describe the pain as passing down the left side of the abdomen below the umbilicus Bleeding may be a serious complication and three of the cases which came into the author s care required immediate operation The condition is associated with loss of weight and there may be a palpable inflammatory mass due to penetration of the ulcer Sudden perforation may be the first indication of the lesion Such an ulcer can usually be seen on barium meal examination or if it extends to the anastomosis it may be visible on gastroscopy Where however there is persistent occult blood even in the absence of confirmatory radiological or gastroscopic findings and the pain is sufficiently severe and unresponsive to adequate medical treatment it is the usual practice to do a laparotomy The procedure to be adopted in such operation depends upon whether the stoma has been or is likely to be stenosed from the presence of a healing or healed ulcer If a large unrestricted stoma is present vagotomy seems to give very good results If a stenosing process is present then a higher gastrectomy or re formation of the stoma must be contemplated with excision of the ulcer and a vagotomy as well

In those cases where gastro jejuno colic fistula supervenes it is wise not to delay surgical treatment It may usually be diagnosed on the incessant diarrhoea faecal vomiting foul eructations and rapidly progressive cachexia Patients may state that the pain of their ulcer has disappeared but the clinical diagnosis can usually be confirmed by the opaque meal or enema both of which should be carried out It is found that an end to side ileo pelvic colostomy (Lahey and Swinton 1935) is the best operation as a primary procedure in these cases This results in side tracking the irritating faecal material which has been passing directly into the jejunum from the colon and giving rise to an irritative jejunitis (Pfeiffer 1939) causing the progressive decline of these patients An ileo pelvic colostomy is a great improvement on the proximal colostomy which is usually recommended in these cases In such a colostomy the faeces are usually fluid leading to excoriation in close proximity to the site of the second stage wound An ileo pelvic colostomy seems to give equally satisfactory results It can be done in these very emaciated cases through a lower left paramedian incision under a local anaesthetic After a few months interval during which the patient will regain his weight and protein balance the second stage can be carried out This consists of dissecting the transverse colon off the anastomosis and closing it over As it is now defunctioned this is usually a fairly easy procedure The surgeon is then left with the alternative of doing a vagotomy or unpicking the anastomosis and doing a high partial gastrectomy exactly as in the operation for simple gastro jejunal ulcer as

described above The third and last stage is to undo the ileo pelvic colostomy and restore the continuity of the ileum In two cases where an ileo-pelvic colo tomy was done the relief has been so great that the second and third stage has been unnecessary as all the unpleasant and dysp ptic symptoms rapidly subsided

THE POST GASTRECTOMY SYNDROME

In recent years considerable attention has b en focused on a group of symptoms which may appear following a gastrectomy and more rarely a gastro enterostomy and seem to be specific to the operation Such symptoms usually occur in a definite time relationship to a meal and have therefore been called the post-cibal or better the post gastrectomy syndrome Others call it the small stomach syndrome In most cases the symptoms are mild and evanescent but sometimes patients are so severely incapacitated that they have been called gastric cripples by Custer Butt and Waugh (1946) As early as 1913 Hurst had noted certain mechanical disturbances following gastro-enterostomy In 1922 Mix described a patient whose ileum had been accidentally anastomosed to the stomach and where rapid emptying of the stomach remnant with pooling of the barium in the intestine occurred To this phenomenon he gave the name of a dumping stomach The term dumping has essentially a radiological connotation and in my cases such a finding on barium meal is by no means always associated with the syndrome For this reason it would be better if the term dumping was abolished from clinical usage and reserved for the pure radiological findings

During the last 3 years especially numerous papers have appeared which have tended to sort out the various symptoms and ascribe to them different causes The assumption that all post-cibal symptoms may be attributed to one cause must be accepted with the greatest reserve The following hypotheses have been offered by various authorities in an endeavour to assess the various factors involved

(1) Rapid emptying of a small gastric remnant with jejunal filling and distension due to absence of a sphincteric mechanism to take the place of the pylorus between the stomach and small bowel (Hurst 1913 Mix 1922 Custer and others 1946 Reingold and Schwartz 1942 Adlersberg and Hammerschlag 1947 1949 Irvine 1948)
(2) Delayed emptying of the stomach remnant (Snell 1937 Hosford 1949)
(3) Reflux of food into the efferent loop of the anastomosis and into the duodenum (Finsterer and Cunha 1931 Ogilvie 1935 Lake 1937 Maingot 1940 Marshall 1944 Wangensteen 1945 Ingelfinger 1944 Monro 1945 Mimpriss and Birt 1948)
(4) Coincident hyperglycaemia due to rapid absorption of carbohydrate (Glaessner 1940)
(5) Reactive hypoglycaemia subsequent to the initial hyperglycaemia (Lawrence 1936 Evensen 1942 Gilbert and Dunlop 1947 Barnes 1947 Adlersberg and Hammerschlag 1947 1949 Zollinger and Hoerr 1947)
(6) Coincident gastro jejunitis (Porges 1947)
(7) Jejunal distension due to osmosis following too rapid entry of hypertonic solutions (Machella 1949)

It was Adlersberg and Hammerschlag (1947) whose findings were confirmed by Zollinger and Hoerr (1947) who really clarified the position by dividing the syndromes into two main groups—an early type coming on within a few minutes of the completion of a meal which they considered due to mechanical factors and a late variety occurring during the second or third post cibal hour and which they regarded as due to a hypoglycaemic phase This division into two main groups has now come to be widely accepted and usually the blood sugar curve together with the time relationship of the symptoms is all that is necessary to distinguish between them

TABLE I

INCIDENCE OF SYNDROME
ACCORDING TO VARIOUS AUTHORS

			%
1	Jordan (Mateer)	1942	12-15
2	Ingelfinger	1944	10
3	Custer and others	1946	20
4	—	1946	5
5	Waugh	1946	12
6	Gilbert and Dunlop	1947	37 7
7	Jordan	1948	8 6
8	Zollinger and Hoerr	1947	5-25
9	Adlersberg and Hammerschlag	1949	6-30

Although many authorities consider that the early syndrome is mechanical in origin there is no general agreement about the exact mechanism Vitkin (1940) stated that in his series the stomach was empty in 20 minutes while Strauss and others (1930) invariably found an emptying time of 50 minutes or less Among other mechanisms held to be responsible are stasis of the bile in the afferent jejunal loop distension of the efferent loop with food distension of the stomach remnant duodenal reflux and too rapid emptying of the stomach with jejunal filling It is the last which seems to hold the field in the view of most observers Rapid emptying occurs virtually after every gastrectomy and therefore it is unreasonable to postulate that it is the cause of symptoms occurring in only a small percentage of cases It would be more rational to suggest (Butler 1950) that rapid emptying and jejunal filling is the cause of the sensation of fullness after meals This symptom following gastrectomy bears a corresponding incidence to the radiological finding of rapid emptying and jejunal filling and moreover can be reproduced by artificial distension of the jejunum with a balloon

In regard to the delayed syndrome there is already considerable uniformity of opinion that it is due to a coincident hypoglycaemia following the initial post cibal hyperglycaemia The work of Lawrence (1936) and Evensen (1942) Lapp and Dibold (1933) Beckermann (1933) Koranyi (1936) Wohrler (1936) Gilbert and Dunlop (1947) and Barnes (1947) affords ample evidence of this Evensen it was who made the significant observation that the hypoglycaemia no longer occurred if the gastro jejunal anastomosis was undone and normal continuity re established

It may be appropriate to compare and contrast the main features of the two syndromes

TABLE II

COMPARATIVE SUMMARY OF ESSENTIAL FEATURES OF EARLY AND DELAYED POST-CIBAL SYNDROMES

		Early Syndrome	*Delayed Syndrome*
1	Incidence	12	5 15
2	Relation to meals	Immediately following meal	During second or third hour after meal
3	Duration of attack	30–40 minutes	30–40 minutes
4	Long Term duration	Severe cases indefinitely	2–5 years
5	Relief by	Rest by lying down	More food
6	Aggravated by	More food	Exercise
7	*Chief precipitating factor*	*Bulk of meal*	*Carbohydrate content of food*
8	Chief symptoms	Epigastri fullness Sweating Sensation of warmth Tachycardia	Tremor Giddiness Epigastric emptiness Nausea
9	Probable nature	Mechanical	Hypoglycaemic

The early syndrome

This syndrome constitutes the major problem as it accounts for the most severe cases It appears when the patient first consumes a meal of moderate bulk following his gastrectomy In a review of 660 cases all of whom had had a partial gastrectomy for benign ulcer Butler and Capper (1951) have attempted to analyse the main features of the syndrome Altogether it occurred in 79 of the 660 cases reviewed (11 9 per cent) Usually the onset is fairly sudden and occurs a few minutes after the meal is finished There is a feeling of distension in the epigastrium and sometimes nausea Vomiting rarely occurs but if it does the patient is usually able to recommence and enjoy a full meal Accompanying these symptoms is a spreading sense of warmth and sometimes beads of perspiration stand out on the forehead and face There is usually a definite pallor and the patient complains of palpitations and a sense of languor or fatigue There is frequently a desire to get to an open window or into the fresh air Sometimes the patients have diarrhoea or borborygmi When the attack first comes on there is considerable apprehension and anxiety on the part of the patient The average attack lasts about 45 minutes and is accompanied by a rise of pulse rate and blood pressure but without any significant changes in the blood sugar level which steadily rises during the occurrence of the symptoms

TABLE III

RELATIVE FREQUENCY OF SYMPTOMS AND SIGNS IN 79 CASES OF EARLY SYNDROME

1	Epigastric fullness and distress	79
2	Pallor	76
3	Failure to gain weight	73
4	Sensation of warmth and lassitude	72
5	Nausea	64
6	Palpitations	50
7	Vomitus of bile stained fluid	41
8	Diarrhoea	10
9	Eructations	9
10	Borborygmi	8
11	Vomiting of food	5
12	Sensation of cold	3

The attacks occur following the heaviest meal of the day and no particular foodstuff can be blamed It is the actual bulk of the meal that constitutes the main factor in precipitating the attack Some patients know exactly how much they can eat with safety, but the extra slice of bread or cup of tea will precipitate the syndrome Thus the patient voluntarily restricts his food intake and this may account for the frequent failure of these cases to gain weight

Forty one of the 79 cases complained of vomiting a thin biliary fluid which was precipitated by changes of posture and especially on stooping down This occurred twice a week or perhaps once every 3 weeks or so Such biliary vomiting may occur entirely apart from the early post gastrectomy syndrome but when it is associated with the syndrome it usually gives considerable relief so that the patient can take much larger meals without ill effect After a few days however the patient finds that smaller and smaller meals cause symptoms and this goes on until the next vomiting attack which again gives relief This may give the early syndrome a cyclical character and it is believed to be due to the gradual accumulation of bile and pancreatic fluids in the afferent loop so increasing the drag on the gastric remnant It is to be noted here that the syndrome has two components (a) a sensation of fullness in the epigastrium and periumbilical area regarded as due to jejunal distension and which occurs in almost every patient who has had a gastrectomy performed (b) vaso motor phenomena (palpitations retching nausea lassitude increase of pulse rate and rise of blood pressure) which form the salient features of the syndrome The majority of patients exhibiting the early syndrome find that if they lie down the symptoms gradually pass off in about 15 minutes In some cases patients actually are forced to eat the main meal of the day lying down to prevent the syndrome occurring Some observers state that the condition usually disappears in 1 or 2 years Custer and others (1946) consider that it lasts indefinitely and Sarah Jordan (1941) observed that it persisted for more than 4 years in 50 per cent of her cases In a series of 79 patients 18 had recovered by the time the investigation was carried out while the remaining 61 (71 per cent) had persistent symptoms from 2 to 11 years It is to be observed also that the symptoms do not all disappear at the same time Usually epigastric fullness disappears first and the vaso motor phenomena may persist for several years afterwards Attempts have been made to assess the severity of the syndrome according to whether it caused loss of work Of the 79 cases 31 were suffering enough to cause periodic loss of work whilst the remainder could manage their daily occupation without interruption on this account

According to our analysis the early syndrome is not a problem following the Billroth I operation but it may occur after any modification of the Polya operation (*see* Table IV) The particular modification does not seriously affect the incidence Certainly it may sometimes occur following the Billroth I operation but only in the 3 or 4 months following operation after which it spontaneously disappears In a sub group of 301 cases where all the operations were carried out by one surgeon the incidence was more or less the same Furthermore there is no particular age or sex incidence of either syndrome early or delayed nor could it be established that it was more or less common according to the site of the ulcer

The effect of the change of posture on the incidence of the syndrome is remarkable In 54 of the 61 cases observed lying down immediately the syndrome occurred

TABLE IV

ANALYSIS OF CASES

	Type of operation		Early syndrome	Delayed syndrome
A	Billroth I	102	—	5 (4.9)
B	Polya antecolic without valve	109	15 (13.7)	6 (5.5)
C	Polya antecolic with valve	168	27 (15.7)	8 (4.7)
D	Polya retrocolic without valve	104	14 (15.6)	6 (5.7)
E	Polya retrocolic with valve	57	8 (14)	3 (5.2)
F	Polya Moynihan (left to right)	120	15 (12.5)	6 (5)
	Total	660	79 = 11.9	34 = 5.2

In this table the subgroups B to F denote operations in which the anastomoses were right to left in type

caused the tachycardia pallor and sweating to disappear within 5 minutes and the sensation of fullness to disappear in 15 minutes Moreover the majority find they can eat a good sized meal lying down though this position has comparatively little effect on the sensation of fullness A certain number of cases vomited a bile stained fluid 30 minutes after food This symptom may occur with or entirely apart from the early syndrome but the vomiting is usually precipitated by changes of posture Where bile vomiting occurred with the early syndrome it was found that after the vomit patients could return and eat a full sized meal without the syndrome occurring This may be accounted for by the stasis of bile in the afferent loop causing a drag on the gastric remnant When the bile has been vomited this factor ceases to operate

Many investigators have commented on various findings on barium meal in these cases Indeed the radiological findings have tended to obscure the more important clinical features and the syndrome has therefore been variously attributed to delayed emptying rapid emptying jejunal distension and afferent loop reflux These may occur with or without the syndrome The significant features however are

(a) that a relatively inert substance such as barium emulsion can produce the syndrome The patients complained of fullness They sweated had palpitations and some of them fainted As many as 79 per cent of the cases had vasomotor symptoms during the radiological examination

(b) In 28 per cent of the cases the symptoms occurred while the barium emulsion was still in the stomach and before it had started to enter the jejunum

(c) In those cases exhibiting the syndrome the gastric stoma descends to a greater degree (an average of 7 centimetres compared with 2 centimetres) on changing from the supine to the erect position Assuming the gastro oesophageal junction to be a fixed point this represents gastric stretching by the weight of its contents

Seeing that it was always the heaviest meal of the day that produced the syndrome it was determined to introduce a Miller Abbott bag into the gastric remnant and fill it with an amount of mercury equal to the weight of the meal

The attacks occur following the heaviest meal of the day and no particular foodstuff can be blamed It is the actual bulk of the meal that constitutes the main factor in precipitating the attack Some patients know exactly how much they can eat with safety but the extra slice of bread or cup of tea will precipitate the syndrome Thus the patient voluntarily restricts his food intake and this may account for the frequent failure of these cases to gain weight

Forty one of the 79 cases complained of vomiting a thin biliary fluid which was precipitated by changes of posture and especially on stooping down This occurred twice a week or perhaps once every 3 weeks or so Such biliary vomiting may occur entirely apart from the early post gastrectomy syndrome but when it is associated with the syndrome it usually gives considerable relief so that the patient can take much larger meals without ill effect After a few days however the patient finds that smaller and smaller meals cause symptoms and this goes on until the next vomiting attack which again gives relief This may give the early syndrome a cyclical character and it is believed to be due to the gradual accumulation of bile and pancreatic fluids in the afferent loop so increasing the drag on the gastric remnant It is to be noted here that the syndrome has two components (a) a sensation of fullness in the epigastrium and periumbilical area regarded as due to jejunal distension and which occurs in almost every patient who has had a gastrectomy performed (b) vaso motor phenomena (palpitations retching nau ea lassitude increase of pulse rate and rise of blood pressure) which form the salient features of the syndrome The majority of patients exhibiting the early syndrome find that if they lie down the symptoms gradually pass off in about 15 minutes In some cases patients actually are forced to eat the main meal of the day lying down to prevent the syndrome occurring Some observers state that the condition usually disappears in 1 or 2 years Custer and others (1946) consider that it lasts indefinitely and Sarah Jordan (1941) observed that it persisted for more than 4 years in 50 per cent of her cases In a series of 79 patients 18 had recovered by the time the investigation was carried out while the remaining 61 (71 per cent) had persistent symptoms from 2 to 11 years It is to be observed also that the symptoms do not all disappear at the same time Usually epigastric fullness di appears first and the vaso motor phenomena may persist for several years afterwards Attempts have been made to assess the severity of the syndrome according to whether it caused loss of work Of the 79 cases 31 were suffering enough to cause periodic loss of work whilst the remainder could manage their daily occupation without interruption on this account

According to our analysis the early syndrome is not a problem following the Billroth I operation but it may occur after any modification of the Polya operation (*see* Table IV) The particular modification does not seriously affect the incidence Certainly it may sometimes occur following the Billroth I operation but only in the 3 or 4 months following operation after which it spontaneously disappears In a sub group of 301 cases where all the operations were carried out by one surgeon the incidence was more or less the same Furthermore there is no particular age or sex incidence of either syndrome early or delayed nor could it be established that it was more or less common according to the site of the ulcer

The effect of the change of posture on the incidence of the syndrome is remarkable In 54 of the 61 cases observed lying down immediately the syndrome occurred

gastro oesophageal junction During the ordinary Polya operation therefore a stout silk ligature was passed around the mass of tissue when ligating the left gastric artery The artery was divided between ligatures below this level for the purposes of resection At the close of the operation the upper angle of the anastomosis was anchored to this ligature This usually gives good support but it may be necessary to stitch the upper two inches of the lesser curve to the right crus and the tissues on the posterior abdominal wall in this region The afferent loop in the right to left operation was slung under the liver by stitching it to the thick rim of peritoneum on the upper edge of the lesser omentum This manoeuvre was found to reduce the incidence of the early syndrome from 13 to 1 5 per cent (*see* Table V)

TABLE V

		No	Early syndrome cases
Series I	Polya Hofmeister No gastric or afferent loop supports	113	15 = (13 2 ,)
Series II	Polya Hofmeister With reconstruction of supports	128	1 (plus 1 ?? doubtful) = (1 5 o)

The difference in the incidence is significant The case mentioned in Series II was a very definite case of the early syndrome Radiological examination showed considerable descent of the stoma and it was therefore assumed that the reconstruction at operation had been inadequate With reference to the doubtful case it was very difficult to decide whether it was a true case or a functional disorder he had many symptoms but no signs except marked afferent loop reflux

When it was found that the syndrome could be prevented by adequate support of the upper stomach it was determined to undertake surgical treatment where severe and crippling disability existed from the syndrome and where the symptoms could be reproduced by the mercury loaded bag Obviously an attempt of this nature could take the form of changing the Polya type to a Billroth I operation Perman (1947) has carried out 25 operations for this purpose with considerable success In Great Britain Murphy (1951) has changed 3 of his cases from the Polya to the Billroth I type in order to cure the syndrome It has been successful in each case Tanner (1951) however has not found it to be satisfactory Butler and Capper have operated on 9 cases and attempted to cure them by supporting the lesser curve and the afferent loop only The abdomen is opened through a mid line or upper left paramedian incision There are usually a moderate amount of filmy or even thick adhesions between the anterior surface of the stomach and the liver At first it may be thought that these would give the required support to the stomach but on dividing them it is obvious that the lesser curve is all the time hanging almost vertically from the cardia the stomach being rotated to the left After the adhesions have been divided the mass of tissue around the left gastric vessels is isolated and ligated by a strong piece of thread leaving the ends long The remains of the lesser omentum are then displayed and especially the thickened fringe of the omentum which lies immediately under the liver This will give a

causing the syndrome It was found that this exactly reproduced the symptoms and that the symptoms were relieved by lying down although the same amount of mercury failed to produce effects in 95 controls *In order to determine the* afferent pathway for these impulses a splanchnic block by the posterior route with procaine was carried out In 77 per cent of cases such a block abolished the *symptoms produced by the mercury loaded bag*

In order to assess the effect of splanchnic block further it has been carried out on all severe cases of the early syndrome as a routine measure In 4 *out of 61 cases* it has given complete relief Forty six patients have been relieved from periods varying between 2 to 9 days According to Mitchell (1938) the sympathetic nerve *supply of the gastro oesophageal area may originate* from the coeliac plexus *via* the left gastric artery or it may receive direct contributions from the splanchnic nerves or from the lowermost thoracic ganglia Obviously therefore splanchnic block will fail to relieve symptoms in those cases where the major sympathetic contribution comes from the splanchnic or thoracic ganglia

The sensation of fullness around the umbilicus after a meal which so frequently follows the operation may be reproduced exactly by the air distension of a balloon situated in the jejunum This occurs in all cases whether they have the syndrome or not It is moreover unaffected by posture but is completely relieved by splanchnic block Furthermore post cibal fullness nearly always disappears after 2 years and its disappearance bears no relation to the vasomotor phenomena which may go on for a number of years longer It seems quite clear therefore that this sensation of fullness is not due to the same cause as the vasomotor phenomena *and should be disassociated from it in the observer s mind*

From a consideration of the anatomy it will be seen that the most fixed parts of the stomach are at its extremities—the gastro oesophageal junction and the pylorus (Barclay 1936 Moody Van Nuys and Kidder 1946) There is further more a very strong peritoneal thickening of the lesser omentum around the left *gastric vessels supporting the upper inch or more of the* lesser curve Thus when the stomach is distended it is the intermittent portion which sags Many observers have remarked that the post gastrectomy syndrome has only occurred of recent years when higher and yet higher gastrectomies are being carried *out A high* gastrectomy necessitates the division of the strong supporting peritoneal bands around the left gastric vessels and the gastro splenic ligament Thus following operation we are left with a small relatively unsupported gastric remnant and hanging from it is the anastomosis together with the U shaped afferent loop *which may furthermore be distended* with pancreatic and biliary juices and possibly afferent loop reflux as well In 37 patients under local anaesthesia traction on the stomach after it has been mobilized produced the sensation of distension in the abdomen *with nausea and retching This* was associated with rise in pulse rate and blood pressure A splanchnic block entirely abolished these symptoms in 26 out of 33 patients Traction on the vagi in these cases appeared to be without any effect at all It seems *probable* therefore *that traction on the* gastro oesophageal junction produced symptoms closely akin to the syndrome *The syndrome* is quite definitely not mediated by the vagus

In view of the above findings it was determined to pay special attention to the support of the lesser curve of the stomach in order to obviate direct drag on the

The late post-gastrectomy syndrome

There is fortunately not so much disagreement about this group of symptoms. They are much less frequent and far less serious than the early variety. The syndrome occurred in 5.2 per cent of 660 cases of gastrectomy which were reviewed (Butler 1951). This incidence is rather lower than that given by other authors for example Gilbert and Dunlop (1947) 37.7 per cent, Evensen (1942) 35.8 per cent.

The syndrome usually commences during the second or third hour after a meal and the onset is rather more gradual than the early type. Typically the symptoms occur at about 11.0 a.m. and 3.0 p.m.—following breakfast and lunch respectively—but may follow any meal. The likelihood of symptoms occurring is greatly increased if the patient is doing work or taking other exercise. The commonest symptoms noted are tremor of the limbs especially the hands, giddiness and profuse perspiration. There is often a feeling of anxiety with associated weakness and exhaustion. Nausea and a feeling of hunger coupled with a sensation of emptiness in the abdomen may also be noted. Complaints of palpitations, headache and a feeling of faintness are frequent and full loss of consciousness sometimes occurs.

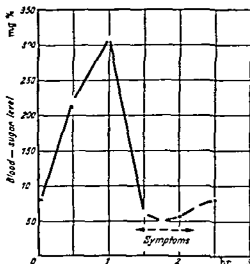


Fig. 186.—Glucose tolerance curve in patient with delayed type of post gastrectomy syndrome.

Examination during the attack reveals tachycardia but the blood pressure changes show a more definite fall than in the case of the early syndrome. Tremor and perspiration are very marked and there is usually obvious pallor. Occasionally the pupils are dilated. Glycosuria and post prandial diuresis may occur and were present in nearly 75 per cent of patients exhibiting the syndrome.

It must be stressed that the syndrome besides following a meal may be seen during the performance of a glucose tolerance curve on the patients in question.

firm bite for sutures to act as a support to the lesser curve A series of thread sutures are then put in every ½ centimetre between the lesser curve and its supporting structures that is first of all the right crus of the diaphragm and from there to this thickened edge of lesser omentum These are tied in order and finally the upper angle of the anastomosis is brought up to the stitch which was left long around the left gastric vessel From this point the afferent loop of the jejunum (in the antecolic Polya right to left operation) is supported by stitching it similarly to the right half of the remaining lesser omentum until the fascia over the common bile duct is reached By this means there is adequate support both for the lesser curve of the stomach and for the afferent loop of jejunum

The patient should be kept lying flat for 3 weeks during the post operative period

Nine such cases have been done in this way and eight of them have obtained complete relief They are able to eat normal sized meals without difficulty again usually they rapidly put on weight and most of them have returned to full work One patient has been a complete failure He found he could take larger meals but complained of symptoms 2 hours later which have not been alleviated

Before these conclusions can be accepted the work of Machella (1949) on the subject must be considered He has carried out a series of interesting and instructive investigations on 20 patients with the early syndrome He reports that the type of Polya operation carried out does not affect the incidence and the symptoms occurred immediately after a mixed meal and were accompanied by a rise of blood pressure and pulse rate during the hyperglycaemic phase He has been able to reproduce the symptoms by oral and intrajejunal hypertonic glucose and sucrose He has found that intravenous glucose does not produce the symptoms but ingestion of a hypertonic protein hydrolysate would do so He was also able to reproduce the symptoms by distending the jejunum with an air inflated balloon He considers the symptoms are due to a marked distension of the jejunum following excessive intestinal secretion induced by a hypertonic solution He noted that vomiting gives relief and he considers the relief that occurs on lying down to be due to the flow back of the jejunal contents into the gastric remnant He was able to show that the dilating mechanism may produce excessive peristalsis thus causing the diarrhoea component of the syndrome He found that balloon distension of the gut sufficient to produce the syndrome always gave rise to pain in the epigastrium and remarked that this symptom does not occur in the syndrome as seen clinically It would be interesting to know if hypertonic solutions cause the syndrome in gastrectomized patients without the syndrome and whether the syndrome occurs on this stimulus if the patient is lying flat It would be thought that all patients who have rapid jejunal filling would experience the syndrome which certainly is not the case Furthermore on this basis the incidence of the syndrome in gastro enterostomy should be the same as in partial gastrectomy Experience of a case where feeding through a jejunostomy tube produced the syndrome almost exactly is known Further investigation of this case is being carried out

In all these experiments it must be pointed out that the great difficulty in interpreting the results of various observers lies in the fact that subjective symptoms of the patient have to be relied on as a basis for argument These obviously vary from hour to hour and day to day in such things as fatigue nervous tension and other factors which cannot be assessed

The late post gastrectomy syndrome

There is fortunately not so much disagreement about this group of symptoms They are much less frequent and far less serious than the early variety The syndrome occurred in 5 2 per cent of 660 cases of gastrectomy which were e viewed (Butler 1951) This incidence is rather lower than that given by other authors for example Gilbert and Dunlop (1947) 37 7 per cent Evensen (1942) 35 8 per cent

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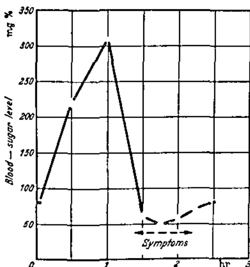


FIG 1°6 —Glucos tolerance curve in patient with delayed type of post gastrectomy syndrome

Examination during the attack reveals tachycardia but the blood pressure changes show a more definite fall than in the case of the early syndrome Tremor and perspiration are very marked and there is usually obvious pallor Occasionally the pupils are dilated Glycosuria and post prandial diuresis may occur and were present in nearly 75 per cent of patients exhibiting the syndrome

It must be stressed that the syndrome besides following a meal may be seen during the performance of a glucose tolerance curve on the patients in question

TABLE VI

FREQUENCY OF SYMPTOMS AND SIGNS OF DELAYED POST CIBAL SYNDROME IN 34 CASES

1	Giddiness	34
2	Perspiration	33
3	Nausea	32
4	Tremor of limbs	29
5	Hunger	28
6	Sensation of emptiness	28
7	Mental change anxiety	24
8	Exhaustion	23
9	Faintness	21
10	Headache	11
11	Paraesthesiae	4

in each case the *symptoms coinciding with the* hypoglycaemia Symptoms frequently commence when the blood sugar value falls to 75 milligrams per cent but they may occur at higher or lower levels (*see* Fig 186) The important factors in the production of the hypoglycaemic symptoms are the maximum fall in the blood sugar level the rate of fall and the minimum value to which it falls

TABLE VII

	Average maximum level of blood sugar	Average minimum level of blood sugar	Average fall in blood sugar	Rate of fall Mg min	No of cases
A Cases with delayed syndrome	231 5 mg	56 8 mg	172 8 mg	3 1	34
B Group of cases without syndrome	149 1 mg	71 4 mg	78 1 mg	1 8	34

Collection of data from the patients indicates that meals or even drinks *with* high carbohydrate content *constitute the chief precipitating factor in the attacks* If the carbohydrate intake is limited the incidence of attacks is markedly reduced

The majority of authors have indicated in their reviews that this syndrome does not appear until 5 or 6 months have elapsed since the operation and Barnes (1947) believes that any explanation of the syndrome must take this fact into account In our series of cases whilst about one third of the cases commenced 1 to 2 months after operation a few actually had symptoms within 3 weeks of the operation Others especially the earlier cases in the series did not get symptoms until some 4 months had elapsed in the post operative period It would appear at least in this series that an *important factor in determining* the times of onset of the syndrome is the change over from 2 hourly diet feeding to meal spacing approaching normal daily routine The earlier *this change takes place after the operation* the sooner

do hypoglycaemic attacks become manifest During the past ɔ years in all my cases of gastrectomy performed for ulcer the establishment of a normal frequency of meals without dietary restriction has been attempted during the first month following operation Whilst on a 2 hourly feed regime hypoglycaemia is not common indeed this is a recognized treatment for the condition Each successive feed corrects the possible hypoglycaemia consequent to the previous meal When a normal routine is re established with a 3 or 4 hour interval b*tween m*als any tend*ncy to hypoglycaemia becomes manifest

There is evidence that the delayed syndrome tends to subside both in intensity and frequency of attacks over a period of 2-5 years In the series of 34 cases studied symptoms in seven cases disappeared within 2 years of their onset whilst in six the syndrome persisted for more than 5 years The longest duration was for 8½ years following the operation

Although very rare patients may exhibit symptoms characteristic of both early and delayed syndromes This was observed in three patients in the whole series

Many views have been put forward to account for the rapid fall in blood sugar levels but the most likely one is that there is a temporary inhibition of glycogeno lysis of the liver due to a transient high portal hyperglycaemia following rapid absorption from the bowel This is based on the fact that following gastrectomy there are two well defined responses to adrenalin demonstrated during the p r formance of a glucose tolerance curve (Butler 1951) In cases without symptoms adrenalin effectively alters the second part of the curve by preventing the rapid fall of blood sugar In patients who exhibit symptoms adrenalin fails to alter the curve and this is interpreted as indicating temporary inhibition of glycogenolysis Hyperglycaemia produced by intravenous glucose of course completely fails to produce subsequent hypoglycaemic symptoms The patients can usually b re assured that the symptoms will completely subside in 2 or 3 years In the meanwhile they should be treated by frequent small meals and the exhibition of ephedrin may relieve the ymptoms In any case most patients find that carrying some sugar around with them to eat as necessary will give adequate control of the condition which is alway self limiting

In conclusion it must be emphasized again that the sequelae which have been outlined here are uncommon and in the vast majority of cases following gastrectomy the patients are well satisfied from every point of view and are entirely without any distressing side effects

REFERENCES

Adlersberg D and Hammerschlag E (1947) *Surgery* 21 7_0
— — (1949) *J Amer med Ass* 7 4 0
Barclay A E (1936) *Digestive Tract* 2nd ed Cambridge Cambridge University Press
Barnes C (1936) *Lancet* 2 536
— (1947) *Ibid* 2 549
Beckermann F (1933) *Dtsch Med Wschr* 59 683
Butler T J (1950) *Ch M Thesis* University of Bristol
— (1951) *Gastroenterol gy* 19 99
— Capper W M (1951) *Brit med J* 1 1177 2 265
Cartwright R W (1947) *Blood* 2 111
Castle W B (19_8) *J Clin Invest* 6 19

Castle W B (1919) *Amer J med Sci* **178** 929
— and Bowie M A (1929) *J Amer med Ass* **92** 1830
— and others (1937) *Amer J med Sci* **194** 618
Custer M D Butt H R and Waugh J M (1946) *Ann Surg* **123** 410
Evensen O K (1942) *Acta med scand Suppl* 126
Finsterer H and Cunha F (1931) *Surg Gynec Obstet* **52** 1099
Gilbert J A L and Dunlop D M (1947) *Brit med J* **2** 330
Glaessner C L (1940) *Rev Gastroent* 7 528
Hartfall S J (1934) *Guy s Hosp Rep* **84** 448
Hosford J (1949) *Brit med J* **1** 929
Hurst A F (1913) *Ann Surg* **58** 466
Ingelfinger F J (1944) *New Engl J Med* **231** 321
Irvine W T (1948) *Brit med J* **2** 514
Jordan S (1941) *J Amer med Ass* **116** 586
Koranyi A (1936) *Dtsch Arch klin Med* **178** 353
Lahey F H and Swinton N W (1935) *Surg Gynec Obstet* **61** 599
Lake N C (1937) *Brit med J* **2** 49
Lapp F W and Dibold H (1933) *Klin Wschr* **12** 547
Lawrence R D (1936) *Brit med J* **1** 526
Machella T E (1949) *Proc Amer Gastroent Ass* June 4th 1949
Maingot R (1940) *Abdominal Operations* London Lewis
Marshall C J (1944) *Proc R Soc Med* **38** 91
Mimpriss T W and Birt J M C (1948) *Brit med J* **2** 1095
Mitchell G A G (1938) *Brit J Surg* **26** 333
Mix C (1922) *Surg Clin N Amer* **2** 617
Monro A K (1945) *Postgrad med J* **21** 228
Moody Van Nuys and Kidder (1946) Quoted by Grant J B *Method of Anatomy* Toronto Baillière Tindall and Cox
Morley J (1928) *Brit J Surg* **16** 239
Muir A (1949) *Ibid* **37** 165
Murphy F D (1951) Personal communication
Ogilvie W H (1935) *Brit med J* **1** 457
— (1938) *Lancet* **2** 295
Perman C (1947) *Acta med scand Supp* **196** 316
Pfeiffer D B (1939) *Ann Surg* **110** 659
Porges O (1947) *Amer J Med* **3** 177
Reingold I and Schwartz A (1942) *Amer J Digest Dis* **9** 151
Snell A M (1937) *Amer J Surg* **35** 45
Strauss H A and others (1930) *J Amer med Ass* **95** 1883
Sturgis C C and Goldheimer S M (1939) *Ann intern Med* **12** 1245
Tanner N (1951) Personal communication
Visick A H (1948) *Ann R Coll Surg Engl* **3** 266
Vitkin S F (1940) *Ann Surg* **3** 27
Wangensteen O H (1945) *Can Med Ass J* **53** 309
Watson A B (1947) *Brit J Surg* **34** 353
Wells C and Welbourn R (1951) Personal communication
Wohrler M (1936) *Dtsch Arch klin Med* **179** 411
Wollager F E (1949) *Proc Amer Gastroent Ass* June 4th 1949
Wright G (1934) *Brit J Surg* **22** 433
Zollinger R M and Hoerr S O (1947) *J Amer med Ass* **134** 575

CHAPTER 19

THE PHYSIOLOGY OF FAT ABSORPTION

A C FRAZER

THE absorptive functions of the small intestine are necessary for life but how these functions are fulfilled is largely unknown The objective of this chapter is to present the available information from which some conception of the mechanism of absorption of one single food material—triglyceride fat—may be derived So far as possible relevant observations and experimental data from studies in human subjects will be used but it is often helpful and may be essential to consider the results of animal experiments or even *in vitro* studies as well Studies in human biology demand the investigation of the abnormal as well as the normal since so frequently only the disease process can provide the experimental situation from which useful data may be derived

So that clinical material can be used for scientific study it is necessary to define as precisely as possible the criteria upon which case selection is based Material selected on some more or less arbitrary clinical classification is usually not suitable for scientific evaluation For the study of fat absorption in man investigations must be carried out not only in normal subjects but also in cases of defective fat absorption The quantitative normality or otherwise of fat absorption could only be satisfactorily determined in man by the use of a fat balance technique (Cooke and others 1946 Black Bound and Fourman 1947) The most useful method was that based on the technique of Kamer Huinink and Weyers (1949) in which the total fatty acid excreted each day in the faeces was determined with the patient on a known fat intake The absorption was calculated as the difference between intake and output—the three-day sliding mean being used to obviate sampling errors Typical normal and abnormal absorption nomographs are shown in Figs 187 and 188 A normal man on a diet containing 50 grams of fat passed about 2–3 grams of fatty material in the faeces At least 50 per cent and possibly all of this was derived from non-dietary sources such as epithelial debris residual material from secretions and bacterial synthesis Thus at least 90 per cent usually 95 per cent or more of ingested fat was normally absorbed In abnormal cases less than 90 per cent was absorbed—abnormality was unquestionable if absorption was 85 per cent or less In abnormal cases there was also usually a marked variation in the amount of fat absorbed from day to day To exclude errors due to fat derived from non-dietary sources the effect of a low fat diet on the faecal fat output was determined The daily fatty acid balance method was particularly useful for this purpose If the increased level of faecal fat persisted on a low fat diet it indicated that this fat was not directly derived from dietary fat Such a state of affairs was recently reported by Kamer and Weyers (1950) in some cases of coeliac disease It was not observed however in adult cases of the sprue syndrome (Cooke and others 1946 Black and others 1947)

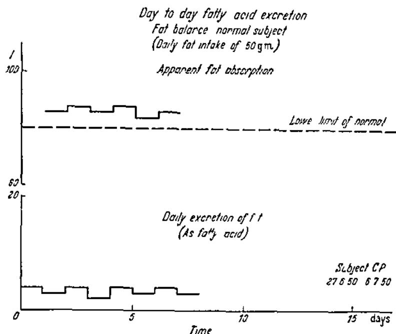


FIG 187 —Normal absorption exceeds 90 per cent daily variations small and regular

Many different clinical conditions are known to be associated with defective fat absorption—including tropical sprue idiopathic steatorrhoea coeliac syndrome pancreatic fibrosis pancreatitis biliary obstruction infective hepatitis gastro colic fistula post gastrectomy syndrome Whipple s disease and regional ileitis For the study of the fat absorption mechanism all but two syndromes must be excluded at present since they cannot be adequately characterized The two syndromes which can be sufficiently precisely defined are a sprue syndrome and a pancreatic syndrome The criteria upon which these two syndromes were diagnosed (Table I) for the investigation of fat absorption are as follows

Sprue syndrome—In addition to a defect of absorption shown by the balance technique described above the following features were regarded as essential for

TABLE I

CRITERIA FOR DIAGNOSIS OF SPRUE AND PANCREATIC SYNDROMES

	Sprue	*Pancreatic*
1 Fat absorption by balance technique – – – – – –	Defective	Defective
2 Pancreatic enzymes by *intestinal intubation method* – –	*Present*	*Absent*
3 Upper intestinal absorptive capacity from glucose absorption curves (intraduodenal drip technique) – – – –	Depressed	Normal
4 Radiographic flocculation pattern – – – – – –	Present	Absent

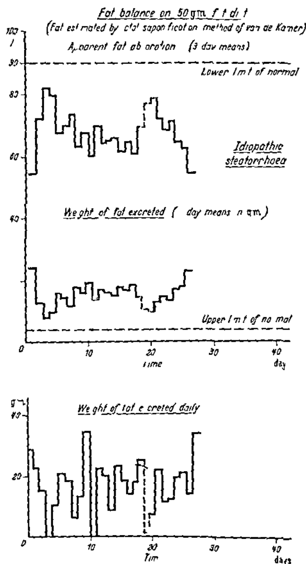


FIG 188 —Defective fat absorption less than 90 per cent daily variations marked and irregular

diagnosis of this syndrome the presence of active amylase trypsin and lipase in the upper intestinal contents demonstrated by intubation (Frazer French Sammons Thomas and Thompson 1949) the *depression of upper intestinal* absorptive function as shown by delayed blood curve for glucose and urea using the intraduodenal drip technique (Frazer and others 1951) increased mucous secretion giving the flocculation pattern radiographically with a simple suspension of barium sulphate in water (Frazer French and Thompson 1949)

Pancreatic syndrome—In addition to the defect of fat absorption shown by the balance technique there was also a marked deficiency of pancreatic enzymes (amylase, trypsin and lipase) *in the upper small intestinal contents* demonstrated by intubation normal upper intestinal absorptive capacity as shown by glucos and urea absorption curves normal mucous secretion as shown by the presence of the feathery radiographic pattern and absence of flocculation

Problems of fat absorption may be conveniently considered in three more or less arbitrary phases The intraluminar phase which includes all the changes which occur after the ingestion of the fat until it is passed through the outer border of *the intestinal cell a cellular phase which includes the mechanism of passage of* the fatty material through the membranes and substance of the intestinal cell and any chemical changes which the fat may undergo in the cell a distributive phase which is concerned with the fatty material after it leaves the intestinal cell until it finally reaches its destination in the body Each of these phases must be considered changes observed in any one phase may be primary or dependent upon changes in some other phase

The available evidence on the mechanism of fat absorption may be grouped in relation to five questions two of which concern the intraluminar phase two the cellular phase and one the distributive phase

How is triglyceride finely emulsified in the small intestine?

That dietary triglyceride was normally emulsified to a particle size of less than 0 5 μ diameter in the upper small intestine was readily demonstrated by intestinal intubation and this observation was in accord *with both animal and in vitro* studies It could also be shown that the *p*H of the intestinal contents averaged 6 5 being usually on the acid side of neutral After feeding fat the *p*H was always acid (Thompson 1948) *In vitro* studies indicated that the only likely system which effectively dispersed triglycerides as a fine oil in water emulsion at a *p*H of 6 5 was the triple combination of lower glycerides fatty acids and bile salts (Frazer and others 1944) It was also demonstrated that except under very exceptional experimental conditions quite *unrelated to those found in the intestine* pancreatic lipolysis resulted in the formation of lower glycerides and fatty acids (Frazer and Sammons 1945 Desnuelles 1948) On the basis of these studies and also from relevant animal experiments it seemed likely that the normal emulsification of triglycerides in man was brought about by this same triple combination—the fatty acids and lower glycerides being provided by hydrolysis of *triglycerides and the* bile salts being added in the bile This was supported by observations on the sprue syndrome and pancreatic syndrome In the former lipase and bile salts were present and emulsification was normal In the latter lipase was absent and there was no effective emulsification If lipase was added to the unemulsified samples

and the material incubated and shaken fine emulsification occurred Further supporting evidence was provided by studies made in cases of biliary obstruction Lipase was present but ineffective and bile salts were absent Faulty emulsification was demonstrated by intubation The addition of the appropriate missing factor in this case bile salts with subsequent incubation and agitation resulted in fine emulsification of the fat (Frazer 1948a) It may therefore be concluded that the presence of lipase and bile in the small intestine is necessary for the fine emulsification of triglyceride fat which depends upon the formation of the triple combination of lower glycerides fatty acids and bile salts

Is the hydrolysis of glycerides partial or complete?

The dietary glycerides were normally hydrolysed by the pancreatic lipase in the upper part of the small intestine As a result of the partial hydrolysis already described fatty acids and lower glycerides were formed which with bile salts caused fine emulsification of the remainder of the fat If pancreatic lipase was absent as in the pancreatic syndrome no emulsification occurred and no hydrolysis of fatty material in the upper intestinal lumen could be demonstrated The fat in the faeces in such cases often showed 80 per cent hydrolysis or more This later hydrolysis of the fat is largely brought about by bacterial lipases and it is clear that the degree of hydrolysis of faecal fat is no guide to pancreatic function which can only be effectively assessed by intestinal intubation (Cooke and others 1946)

When lipolysis was studied *in vitro* the reaction came practically to a stop when some 20 per cent of fat had been hydrolysed and as already described the end products were di and mono glycerides and fatty acids The reason for this early cessation of hydrolysis was that the oil water interface at which the lipase must act became blocked by accumulated end products which displaced the enzyme (Frazer 1948b) Lipolysis could only continue if these end products were removed into the water phase This might be achieved in four ways—short-chain fatty acids such as butyric acid being water soluble were readily removed and did not block the interface long-chain fats might be removed either as soap or possibly as a water soluble complex with bile salts while mono and di glycerides might be converted into phospholipid and so become molecularly dispersed in the water phase The hydrolysis of the short-chain glycerides is therefore likely to be unrestricted in the intestinal lumen but the questions of available base and *p*H bile salts and phosphorylation must be considered in relation to the hydrolysis of long-chain triglycerides

It has been argued that hydrolysis of fats is more complete *in vivo* than *in vitro* because the products of hydrolysis are rapidly absorbed from the intestine For this argument to have any substance it must be assumed that the fatty acid is already molecularly dispersed in the water phase Experimentally no significant quantity of fatty acid was removed from the oil into the water phase at *p*H 6 5 The formation of significant quantities of soap in which form the fatty acid must be removed into the water phase is made even more improbable under the actual conditions which prevail in the intestinal lumen since the fatty acid has to compete for available base with gastric hydrochloric acid In the absence of gastric hydrochloric acid more extensive soap formation is clearly possible

It was suggested by Verzár and Kuthy (1931) that bile salts had a hydrotropic

action on fatty acids bringing them into solution in water This hydrotropic effect has not however been fully substantiated by subsequent observers (Breusch 1937 Vonk, Engel and Engel 1938 Verkade 1948) In any case as pointed out originally by Verzar the amount of bile salts available was not sufficient to account for the quantities of fat known to be absorbed He therefore postulated the absorption of bile salts on to the intestinal cell surface from which point they were alleged to exert their hydrotropic effect on the fatty acids Again this avoided the essential issue of the removal of the fatty acid from the oil phase Experimentally bile salts did not bring about this molecular dispersion at any physiological concentration

If the intraluminar emulsion was examined it was found to give the flocculation reaction associated with a simple negatively charged emulsion (Elkes Frazer Schulman and Stewart 1945) For this reason and since it was not affected by C lecithinase and phospholipid could not be demonstrated by chemical analysis it was concluded that phospholipid was not an essential part of the intestinal emulsifying system (Frazer 1949a) It was also suggested that in the intestinal lumen no significant quantity of fatty material was removed from the oil into the water phase as phospholipid Furthermore no lecithinases could be demonstrated in the intestinal contents or digestive juices of rats dogs or man although an effective C lecithinase was found in an extract of rat s intestinal mucosa and in some samples of pancreatin (Frazer Sammons and Sagrott 1949) Although phospholipid formation may have some part to play in the fat absorption mechanism—possibly in the cellular phase—there was no evidence to suggest that it played any important role in the intraluminar phase

The recent work of Favarger (1950) contributed more direct evidence on this question of the extent to which hydrolysis of triglycerides occurred *in vivo* Using deuterium labelled glycerol and C_{14} labelled fatty acids which he administered to rats during the absorption of long chain triglycerides such as trielaidin Favarger has shown that less than 4 per cent of glycerides re formed in the intestine contained the labelled glycerol From these and other studies using labelled fatty acid he concludes that the hydrolysis of the triglycerides in his experiments did not exceed 30 per cent and that at least 90 per cent of the fatty material was absorbed in the form of glycerides

It must be concluded from these various observations that the hydrolysis of long chain glycerides is likely to be restricted under the conditions which normally prevail in the lumen of the upper small intestine Glycerides containing short chain fatty acids might be more rapidly and completely hydrolysed

This conclusion was borne out by extensive experiments both in animals and *in man* These studies show in various ways that significant differences exist between the absorption of glycerides containing long chain and those containing short chain fatty acids and also that different sequelae occur following the absorption of fatty acids as compared with those resulting from the absorption of similar quantities of glycerides containing the same fatty acids It is difficult to reconcile these observations with the concept that all glycerides must be completely hydrolysed to fatty acids and glycerol prior to absorption

The absorption of a long chain triglyceride was associated with fine emulsification of the fatty material in the intestinal lumen heavy staining of fat globules in the intestinal cells milkiness of the intestinal lymphatics passage of fat laden chyle up

the thoracic duct the development of a characteristic post absorptive systemic hyperlipaemia and the deposition of the fatty material in the fat depots The absorption of long-chain triglycerides was depressed by double adrenalectomy in the rat (Verzar and Laszt 1935 Barnes Miller and Burr 1941) The absorption of tributyrin on the other hand was not associated with fine emulsification in the intestinal lumen there was no milkiness of the intestinal lymphatics (Daniel and Frazer 1951) and no tributyrin could be demonstrated in the chyle (Hughes and Wimmer 1935) or in the fat depots (Davis 1930) Absorption of tributyrin was not depressed by double adrenalectomy in the rat (Bavetta and Deuel 1942) The observations with tributyrin were similar to those observed following the absorption of long chain acids (Frazer 1943)

Quite different sequelae are observed if fats are fed to animals or to man as fatty acids or as glycerides containing the same fatty acids Thus instead of the characteristic changes in the fat content of the chyle the systemic blood and the fat depots observed during glyceride absorption fatty acid absorption may occur without any alteration in these tissues but the accumulation of fatty material was demonstrated in the liver These original observations (Frazer 1938 1943) were the first indication that there might be two forms and possibly two routes of absorption for fatty material They also threw some doubt on the view current at that time that glycerides had to be hydrolysed to fatty acids before absorption of the fat could occur The studies on fatty acid absorption were not intended to be directly relevant to problems of normal absorption which are essentially concerned with the ingestion of glycerides and the absorption of fatty material derived from this source in the intestinal lumen

Certain other sequelae associated with the absorption of glycerides or of fatty acids also differed Thus glyceride absorption usually had little effect on the emptying time of the stomach or gastric acidity but fatty acid invariably caused marked delay in emptying and inhibition of gastric secretion Glyceride usually had no apparent effect upon intestinal mucous secretion in animals while the fatty acids contained in the glyceride caused a marked increase of secretion Similar observations on gastric movement and secretion were demonstrated in man In experimental studies in human subjects it was shown that the so-called deficiency pattern of the small intestine (Golden 1945) demonstrable radiographically could be induced in normal human subjects by the administration of fatty acids and certain other substances but not by the giving of glycerides in similar quantities The pattern was shown to be due to flocculation of the barium sulphate suspension by mucus (Frazer French and Thompson 1949) Further confirmation was afforded by experiments with non flocculating forms of barium sulphate which visualized the normal feathery pattern of the intestine under the same conditions (Ardran French and Mucklow 1950) Thus administration of fatty acid in man was associated with increased mucous secretion and the radiographic flocculation pattern while the absorption of glycerides was not

The significance of these differences following the administration of glycerides or their constituent fatty acids was reinforced by studies on the sprue syndrome and the pancreatic syndrome In the sprue syndrome there was normal emulsification and the pancreatic enzymes were present but there appeared to be some delay in or depression of the normal absorptive activity of the upper intestine It might be

expected therefore that glyceride absorption might be delayed and that more extensive hydrolysis than normal might occur If this were so sequelae associated with fatty acid absorption should begin to become evident It may be significant therefore that all these cases showed the radiographic flocculation pattern indicative of increased mucous secretion That this radiographic pattern in the sprue syndrome was due to increased mucous formation was confirmed by the fact that the flocculation pattern was no longer observed when a type of barium sulphate suspension was used (for example Raybar) which did not flocculate with mucus Subsequent re examination using normal watery suspension of barium sulphate which was flocculable with mucus again revealed the typical flocculation pattern (Ardran French and Mucklow 1950) There was also evidence of delayed emptying time of the stomach and decreased gastric acidity in most cases of the sprue syndrome It would seem reasonable to suppose therefore that the sprue syndrome was at least in part due to a change over from glyceride to more extensive fatty acid absorption and that this change was occasioned by the demonstrable delay in upper intestinal absorption (Frazer 1949b) The pancreatic syndrome offered a clear contrast In these cases there was again defective absorption but there was no effective lipolysis in the upper intestine as shown by intubation Consequently there was none of the effects associated with increased fatty acid formation in the upper intestine—the radiographic pattern gastric emptying time gastric acidity and the absorptive functions of the upper intestine were apparently normal If large quantities of pancreatin were administered the radiographic flocculation pattern was induced (Lowe May Stauffer and Neuhauser 1950) This might have been due to increased fatty acid formation in the upper intestine following the administration of lipase

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Does fine emulsification of fat in the intestinal lumen play an essential part in the normal mechanism of absorption?

The fine emulsification of fat in the small intestine has been generally regarded as merely a preliminary to more rapid and complete hydrolysis—the greatly increased surface of oil exposed to the action of the enzyme assisting towards this end However even with fine dispersion the oil water interface was blocked by end products before hydrolysis had far advanced Further it has already been concluded that hydrolysis in the upper intestinal contents is normally partial and not complete The question therefore arises whether this fine emulsification has some other function in the absorptive mechanism and especially whether it may be concerned in the ab orption of unhydrolysed or partly hydrolysed glycerides which are not water soluble

The fatty material in the intestinal lumen must first come into contact with the

outer border of the intestinal cell and the structure of this outer border has been and still is the subject of some controversy It is generally agreed that the outer 2 μ approximately of the absorbing cells of the small inte tine possess different refractile properties from the rest of the cell This outer edge of the cell has been called the brush or striated border since it has a striated appearance running perpendicular to the surface of the mucous membrane Baker (1942) has put forward convincing evidence that this outer border of the cell is pierced by fine canals running at right angles to the surface He has demonstrated these canals in both longitudinal and transverse section in fresh specimens and after using several diff rent methods of fixation His main findings have been confirmed by Williams (1949) Baker and Granger (1950) using the electron microscope have demonstrated that the outer border consists of fine villus like projections and their photographs do not show many open canals like those seen in Baker s (1942) preparations However their material consists of extremely thin sections (0 5–0 2 μ) of ileum and a more extensive study of other parts of the intestine is required before any definite conclusions can be reached While further studies are clearly necessary to establish the precise morphology of this part of the intestinal cell– none of the recent evidence so far available is incompatible with the occurrence of particulate absorption—fat particles appear to pass through the inner border of the intestinal cell and through many other cell membranes which have never been shown to have any specialized canalicular structure While the demonstration of canals in the outer border of the intestinal cell may be a significant factor in relation to the mechanism of fat absorption it is experimental studies on absorptive function which must decide whether particulate absorption does in fact occur

Much evidence has accumulated indicating that fine division of oil is an important factor in absorption of the water insoluble fraction Thus it was shown that paraffin passed into the intestinal cell provided that it was pre-emulsifi d to a particle size of less than 0 5 μ and that these particles were negatively charged Particles of a similar size but positively charged did not pass into the cell Paraffin alone was not absorbed since being unhydrolysable it was unable to provide either the fatty acid or the monoglyceride essential for fine emulsification in the intestinal lumen (Frazer Schulman and Stewart 1944) This was supported by the work of Molander (1949) Lundbaek and Maaloe (1947) however did not succeed in repeating these observations There are however many possible reasons for this negative finding Finely di persed paraffin emulsions with a particle size of less than 0 5 μ are difficult to prepare and a particle size of 0 5 μ or more will effectively prevent absorption—this size factor is most critical Paraffin emulsions can never improve as olive oil emulsions do since hydrolysis of the olive oil produces potent emulsifying agents but the paraffin is unhydrolysable Paraffin emulsions from the moment they are prepared can only deteriorate Even if the emulsions used are adequately dispersed particulate absorption may be prevented by various intestinal factors such as excessive mucous secretion This condition may be present due to dietary or other factors or it may be induced by the presence of free fatty acid (Frazer French and Thompson 1949) which may be used as stabilizer in the emulsion The experiments of Berry and Ivy (1950) which the authors claim confirm those of Lundbaek and Maaloe have little relevance to these problems The animals used were dogs the residual extraction from the

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intestinal lumen was carried out with fat solvents and the whole intestine was minced and extracted so that these experiments can supply no information on the question of the passage of particulate paraffin through the outer border of the intestinal cell The problems of obtaining and maintaining fine emulsification of paraffin and the possible existence of conditions in the intestinal lumen unfavourable to particulate absorption apply with equal force in these experiments

Several different groups of investigators have demonstrated that paraffins including isotope labelled hexadecane can be absorbed (Channon and Collinson 1929 Twort and Twort 1932 Channon and Devine 1934 Stryker 1941 Stetten 1943) but the precise conditions determining this absorption have not yet been adequately defined It is clear however that no system is known that will bring these paraffins into solution in water Therefore a possible relationship of paraffin absorption to solubility in oils may be significant It was shown that 60 $\pm$ 5 per cent of the paraffin contained in a mixture of equal parts of paraffin and olive oil disappeared from the intestinal lumen in acute experiments in rats and 64 per cent in long term feeding studies The amount of paraffin absorbed by each rat in the acute experiments was 120–150 milligrams and in the long term experiments 10 rats absorbed 108 grams of paraffin in 16 days This absorption only occurred when a low viscosity paraffin was used which was *completely miscible with olive oil so that the mixture of paraffin and oil was* finely emulsified on hydrolysis (Daniel Frazer French and Sammons 1951) The possible importance of mutual solubility of paraffin and oil in absorption studies is being further investigated but the observations made so far are in accord with other experimental studies on castor oil and long chain fatty acids and esters

If castor oil alone was administered fine emulsification of the oil did not occur in the lumen of the small intestine The oil passed into the lower parts of the bowel and catharsis occurred If the castor oil was mixed with olive oil or corn oil fine emulsification occurred and the castor oil was almost completely absorbed without any cathartic effect (Frazer French and Sammons 1949) Stearic acid fed alone was poorly absorbed but the addition of olive oil increased absorption to about 95 per cent Methyl esters of higher fatty acids were not emulsified to any extent in the intestine of the fasted mouse Small amounts of corn oil or monopalmitin promoted emulsification *The absorption of methyl esters was subnormal in the* fasting mouse but was brought to normal levels by the addition of these glycerides (Mead Bennett Decker and Schoenberg 1950) It would appear from these various observations that the absorption of many substances was dependent upon their solubility in glycerides The absorption of glycerides and therefore of these substances also appeared to be related to fine emulsification in the intestinal lumen This fine emulsification may enable the glycerides and substances soluble in glycerides to enter the outer border of the intestinal cell and thus come into a more intimate relationship with the cell cytoplasm

The importance of glycerides in the absorption of long chain saturated fatty acids is further supported by studies in the sprue syndrome In this syndrome the absorption of fat may be mainly in the form of fatty acid instead of glycerides If this is so it might be expected that dietary fats containing more saturated long chain fatty acids would be poorly tolerated and that the faecal fat would contain

a high proportion of long-chain saturated fatty acids since under normal circumstances these would be absorbed in the form of or dissolved in glycerides Patients with the sprue syndrome did not tolerate meat fat which has a high content of saturated long chain fatty acids as well as olive oil which has a lower content The fats occurring in the faeces in the sprue syndrome were largely saturated long chain fatty acids which may be seen in the faeces as sheaves of crystals This was noted by Parsons (1932) and has been studied more extensively by Kamer (1949) In the pancreatic syndrome there was gross interference with absorption of glycerides which could be attributed to the lack of fine emulsification demonstrated by intubation In these cases the upper intestinal absorptive capacity was normal The introduction of finely emulsified vitamin A into the duodenum in cases of pancreatic fibrosis resulted in improved absorption and a normal plasma vitamin A curve (May and Lowe 1948) This clearly indicated that fine emulsification had some other relationship to fat absorption than preparation for more complete hydrolysis since in these cases there was no demonstrable lipase in the upper intestine

It may be concluded from these observations that there are two forms in which fat is absorbed—a water soluble form and a water insoluble form the former being essentially fatty acids and soaps and the latter glycerides With regard to the absorption of glyceride fine emulsification to a particle size of less than 0 5 μ and the presence of a negative charge on the particles appears to be important From the present evidence on the structure of the intestinal cell it seems likely that fine emulsification may determine the entry of the particulate glycerides into the outer border of the intestinal cell

Does phospholipid formation play an important part in the fat absorption mechanism?

It is generally agreed that phospholipid mainly lecithin is formed in the intestinal cells during fat absorption (Sinclair 1929 1936 Artom and Peretti 1935 Perlman Ruben and Chaikoff 1938 Hahn and Hevesy 1938) but it has been claimed from more recent studies that only a small amount of phospholipid may be formed (Schmidt Nielsen 1946 Zilversmit Entenman and Chaikoff 1948) In the earlier experiments the various components were administered by mouth whereas in the later experiments the radio active phosphorus was given parenterally It seem likely that raw material for synthesis in the ab orbing cells of the small intestine would come from the intestinal lumen If this is so conditions in some recent experiments may be such that phospholipid formation was restricted This does not invalidate the carefully worded conclusion of Chaikoff and his colleagues that phospholipid did not appear to be an obligatory intermediate in fat absorption in their experiments From all these studies it may be concluded that phospholipid is formed during fat absorption but that the quantity may be small without any apparent effect on the absorptive mechanism

Verzar and his colleagues were largely responsible for the view that phospholipid formation was an important step in the fat absorption m chanism Their argument was based upon four main points—the effect of adrenalectomy and the effect of intoxication with monoiodoacetic acid or phloridzin on fat absorption the cause of defective glucose absorption and vitamin B d ficiencies in sprue and the

action of glycerophosphates on fat absorption The relationship of much of this evidence to phospholipid formation has not however been substantiated by subsequent work

Doubly adrenalectomized rats absorbed only about 50 per cent of triglycerides administered instead of the normal 95 per cent or more (Verzar and Laszt 1935 Barnes Miller and Burr 1941) Tributyrin on the other hand was normally absorbed (Bavetta and Deuel 1942) and so also were fatty acids (Frazer 1948a) Stillman Entenman Anderson and Chaikoff (1942) were unable to demonstrate any change in phospholipid turnover in the intestinal cells after double adrenalectomy Barnes and others showed that fat absorption returned almost to normal with adequate salt the apy The available evidence therefore seems to indicate that changes associated with double adrenalectomy esp cially those affecting water and electrolytes interfere with the absorption of long chain fats The interference affected glyceride rather than fatty acid absorption There was no evidence that these effects were due to decreased phospholipid formation

Large doses of moniodoacetic acid were said to cause interference with fat absorption (Verzar and Laszt 1934) These effects were studied by the detailed method combining both biochemical and histological examination in the same animal About 800 of the 900 milligrams of the fat administered were retained in the stomach The remaining 100 milligrams were found to be lying within the cells and corium of the villi If the residual material from the intestine was washed out with a fat solvent as described by Verzar all this fatty material was recovered but if water was used the true state of affairs was immediately apparent The main action of moniodoacetic acid in these experiments appeared to be due to depression of gastric and intestinal motility (Frazer 1948a) The phloridzin experiments in which massive doses had to be used to produce an effect on fat absorption require further study Schmidt Nielsen (1946) showed that intoxication with moniodoacetic acid at this dosage level did not alter the phospholipid turnover in the intestinal cells

It was argued by Verzár and his colleagues that faulty phosphorylation was a common factor which determined the presence of defective absorption of fat glucose and certain B vitamins in sprue However if the absorption of both glucose and urea was studied in cases of the sprue syndrome urea absorption was found to be decreased in an exactly similar manner to glucose absorption (Frazer French and Thomas 1951) It seemed probable that the defective absorption of these two substances was due to mechanical interference with absorption rather than faulty phosphorylation The vitamin B deficiencies in the sprue syndrome were peculiarly selective—aneurin deficiency being rare while nicotinic acid and riboflavine deficiencies were relatively common There was no evidence of faulty utilization of these vitamins since small doses were usually effective when given parenterally Again the evidence favoured mechanical interference with absorption possibly due to successful competition for these nutrients by intestinal bacteria (Frazer 1949c) rather than a phosphorylation fault

The addition of glycerophosphate (Verzar and McDougall 1936) lecithin (Augur Rollman and Deuel 1947) and choline (Frazer 1950) increased the amount of fat absorbed in 4 hours Whether this was due to increased formation

of phospholipid has not yet been established These observations serve to emphasize the importance of considering the possible part which other dietary constituents may play in the normal absorptive mechanism That materials absorbed from the intestinal lumen into the intestinal cells could be incorporated into the phospholipids leaving the intestine was shown by the early experiments of Sinclair (1929) and Artom and Peretti (1935) It was suggested by Sinclair that this phospholipid formation was a necessary intermediate step in the re synthesis of triglycerides

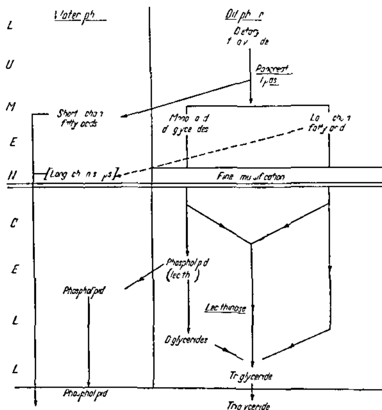


FIG 189 —Diagrammatic representation of some of the possible inter relationships of glycerides fatty acids and phospholipids during absorption. The effect of water or oil solubility is also indicated

from fatty acids and glycerol Synthesis of triglycerides can occur *in vitro* however without any intermediary phosphorylation If hydrolysis is only partial instead of being complete re synthesis of triglycerides may be from lower glyceride rather than from fatty acids and glycerol It is clear that triglycerides or phospholipids must be formed in the intestinal cell from mono- and di glycerides and fatty acids since these substances are not found in the chyle (Frazer [illegible]

observations by Bergstrom and others (1950) would seem to support this A potent C lecithinase can be demonstrated in extracts of intestinal mucosa *in the rat but* no lecithinases were found in any of the intestinal juices or in the intestinal contents (Frazer Sammons and Sagrott 1949) It would appear that lecithin is absorbed into the intestinal cell without undergoing chemical modification Some of the possible relationships of fatty acids glycerides and phospholipids during absorption are indicated in Fig 189

The accumulation of lecithin in the intestinal cell whether it is derived from pre *formed lecithin absorbed unchanged* or from lecithin synthesized from lower glycerides or other suitable raw materials within the cell appears to increase the rate of absorption of fats possibly *due to alteration in the lipophilic properties* of the cell cytoplasm Whatever may be the action of phospholipid formation on the fat absorption mechanism the accumulation of lecithin in the *intestinal cell* must be dependent upon the supply of lecithin or raw materials for synthesis and the activity of lecithin synthesizing and destroying enzymes Until more information is available the part played by phospholipid formation in the fat absorption mechanism must be left open

Is there an alternative pathway to the lymphatic route for the absorption of fatty *material?*

There is no doubt that during the normal absorption of long chain triglycerides *most of the absorbed fatty material passes up the thoracic duct in the chyle In* the classical experiments of Munk and Rosenstein (1891) in which they studied fat absorption in a girl with a lymphatic fistula some 60 per cent of the fat ingested was recovered On the whole this was a reasonably high level of recovery considering the conditions of this experiment and it is doubtful whether the failure to collect some 40 per cent should be regarded as indicating the passage of fat by any alternative route Using the technique described by Bollman Cain and Grindlay (1948) over 80 per cent of ingested triglyceride was recovered from the chyle in rats (Bloom Chaikoff Reinhardt Entenman and Dauben 1950) On the other hand tributyrin cannot be traced *into the chyle or into the fat depots and* if oleic acid alone is fed there may be marked deposition in the liver (Frazer 1943) *Under normal circumstances the* fatty acids which can be removed most easily into the water phase are the short chain fatty acids and these are certainly absent from fats passing up in the chyle While some of them may be built up into other fats it is probable that some may pass like other water soluble substances into the portal blood Long chain fatty acids especially of the saturated series if fed with glyceride will of course be carried in the oil phase and such acids *are likely* to be taken up into triglycerides

Bloom and *others (1950) and also Bergstrom and others* (1950) have mis placed the emphasis in their interpretation of the results of earlier studies on *fatty acid* ab orption (Frazer 1943) in which differences were demonstrated between the absorption of fatty acids on the one hand and glycerides containing the ame fatty acids on the other The demonstration of these differences has since been greatly extended especially in relation to studies in human subjects (*Frazer* 1948a 1949b 1950) The essential point at issue was whether hydrolysis of glycerides was complete as has *been stated by all authorities writing* on fat

absorption from 1900–39 or whether it was only partial In the course of these experiments it was observed that certain fatty acids appeared to pass under the experimental conditions prevailing in these experiments by some other route than the thoracic duct It seemed possible that one of the factors determining this partition was whether the material was water soluble or whether it was present as negatively charged particles of oil dispersed in the water phase It was clear from the beginning that the absorption of oleic acid fed alone was likely to be different from the absorption of palmitic and stearic acid or even oleic acid itself when the acid was dissolved in the oil phase of a glyceride emulsion In recent work on the sprue syndrome (Frazer 1949b) the difficulties of absorbing long chain saturated fatty acids alone as compared with their absorption as part of or dissolved in glycerides has been emphasized The observations of Bloom and others (1950) and of Bergstrom and others (1950) on the absorption of labelled palmitic and stearic acids dissolved in olive oil or corn oil are in complete accordance with the partition hypothesis for in normal rats these long-chain saturated fatty acids would be expected to accompany the glycerides or fail to be absorbed In a condition such as the sprue syndrome glyceride absorption is decreased and fatty acid absorption increased with a resultant increase in long chain saturated fatty acids in the faeces There is no doubt that short chain fatty acids disappear from the fatty material during the course of its absorption They are present particularly in milk fats but they are not found in the fatty material in the chyle nor are they deposited in the fat depots It has already been shown how these short chain fats are more easily removed from the oil into the water phase It is likely therefore that they are absorbed in molecular dispersion in water This is borne out by the studies made in the extreme case of tributyrin

What happens to these short chain fatty acids? No doubt some of them are utilized for synthesis of other materials in the intestinal cell It would be surprising if some of them did not pass with other water soluble materials in the portal vein and there is some evidence that this may be the case (Raper 1913) More difficult still is the question of unsaturated fats—are they dealt with as long chain fats or as short chain fats? There is some evidence that oleic acid may be treated either way and under certain circumstances this acid may pass in the portal vein to the liver (Frazer 1943) Under normal circumstances it appears that most of the oleic acid passes up in the chyle as glyceride but if the particulate mechanism of absorption is interfered with as may be the case in the sprue syndrome it would seem that oleic acid may be more easily absorbed than more saturated fatty acids of similar chain length

On present evidence it would appear that there may be an alternative pathway for absorption which is probably the portal vein Under normal circumstances most of the saturated long-chain fats pass up in the chyle and probably most of the unsaturated long chain fatty acids also Short chain fats clearly do not pass into the body by this route and they are either utilized for synthesis of other compounds in the intestinal cell or pass into the body *via* the portal blood—probably both Under abnormal circumstances if the absorption of glycerides is delayed or prevented more extensive use of the portal pathway may be made

Summary of the mechanism of fat absorption

To summarize the present situation with regard to fat absorption the probable mechanism of absorption is illustrated in Fig 190 This takes into account both earlier and more recent work on fat absorption and the hypothesis provides an explanation for most of the main observations in this field As will be seen the working hypothesis put forward is in fact the partition hypothesis (Frazer 1938

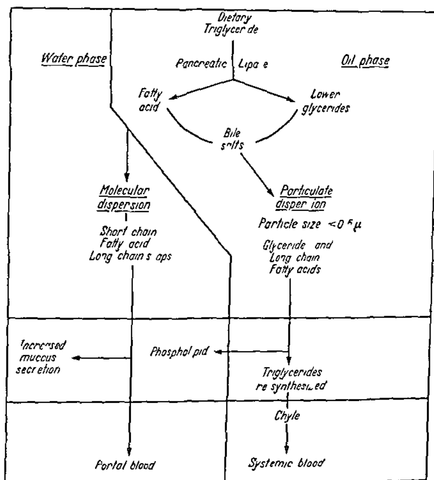


FIG 190—The Partition Hypothesis of Fat Absorption Hydrolysis of dietary triglyceride need not be complete for absorption to occur This leads to the absorption of two forms of fatty material—one water soluble and the other water insoluble—each requiring a different mechanism and causing different effects

1940 1946) with certain elaborations based on recent work no major modifications of the original hypothesis have so far been required The essential points are partial hydrolysis of the fat giving rise to fatty acids and lower glycerides fine emulsification of the glyceride residue by the triple combination of lower glycerides fatty acids and bile salts removal of some fatty acids especially short-chain

compounds into the water phase passage of negatively charged finely dispersed glyceride particles into the outer border of the intestinal cell the formation of phospholipid from lower glycerides the passage of water soluble and water insoluble fatty material into the cell the re formation of triglycerides the passage of particulate triglyceride into the chyle the utilization of water soluble fatty material for synthetic processes or its passage into the body mainly by the portal route There are thus two different forms involving two different m chanisms in which fatty material may be absorbed and there are two different routes by which the absorbed fatty material may pass into the body The nature of the fat ingested the intraluminar conditions and possibly the activity of the intestinal cells may each play a part in determining the proportion of fat absorbed as fatty acid or as glyceride

REFERENCES

Ardran G M French J M and Mucklow E H (1950) *B it J Ra liol* 23 697
Artom C and Peretti G (1935) *Arch int Physiol* 42 61
Augur V Rollman H S and Deuel H J Jun (1947) *J Nutrit* 33 177
Baker J R (1942) *Quart J micr S i* 84 73
Baker R F and Granger B (1950) *Anat Rec* 107 423
Barnes R H Miller E S and Burr O (1941) *J biol Chem* 140 241
Bavetta L A and Deuel H J Jun (1942) *Amer J Physiol* 136 712.
Bergstrom S Borgstrom B Carlsten A and Rottenberg M (1950) *Acta chem scand* 4 1142
Berry I M and Ivy A C (1950) *Amer J Physiol* 162 80
Black D A K Bound J P and Fourman L P R (1947) *Quart J Med* 40 99
Bloom B Chaikoff I L Reinhardt W O Entenman, C and Dauben W G (1950) *J biol Chem* 184 1
Bollman J L Cain J C and Grindlay J H (1948) *J Lab clin Med* 33 1349
Breusch F L (1937) *Biochem Z* 293 880
Channon H J and Collinson G A (1929) *Biochem J* 23 676
— and Devine J (1934) *Ibid* 28 467
Cooke W T Elkes J J Frazer A C Parkes J Peeney A L P and Sammons H G (1946) *Quart J Med* 39 141
Daniel J W and Frazer A C (1951) Unpublished data
— — French J M and Sammons H G (1951) *J Physiol* 114 26
Davis R E (1930) *J biol Chem* 88 67
Desnuelles P (1948) *Biochimica biophys Acta* 2 561
Elkes J J Frazer A C Schulman J H and Stewart H C (1945) *Proc R Soc A* 184 10?
Favarger P (1949) *Helv physiol pharmacol Acta* 8 C15
— (1950) *A ch sci phys* 3 59
Frazer A C (1938) *Analyst* 63 308
— (1940) *Physiol Rev* 20 561
— (1943) *J Physiol* 102 306 329
— (1946) *Physiol Rev* 26 103
— (1948a) *Arch sci phys* 2 15
— (1948b) *J R Soc Arts* 96 582
— (1949a) In *Surface Chemistry* p 241 London Butterworth
— (1949b) *B it med J* 2 769
— (1949) *Ibid* 2 731
— (1950) In *Mod rn T ends in Paediat ics* p 528 London Butterworth
— Schulman J H and Stewart H C (1944) *J Physiol* 103 305
— and Sammons H G (1945) *Biochem J* 39 122
— French J M and Sammons H G (1949) *Proc I Internat Congr Biochem*
— — and Thompson M D (1949) *Brit J Radiol* 22 123
— Sammons H G and Sagrott P E (1949) *Proc I Internat Cong Bioch m*

Frazer A C French J M Sammons H G Thomas G and Thompson M D (1949) *J Nutrit* 3 358 363
— — and Thomas G (1951) Unpublished data
Golden R (1945) *Radiologic examination of the small intestine* Philadelphia Lippincott
Hahn L and Hevesy G (1938) *C R Lab Carlsberg* 22 188
Hughes R H and Wimmer E J (1935) *J biol Chem* 108 141
Kamer J H van de (1948) Vet in Faeces *Ph D Thesis* University of Utrecht
— Huinink ten B and Weyers H A (1949) *J biol Chem* 177 347
— and Weyers H A (1950) Centraal Instituut voor Voedingsonderzoek T N O , Utrecht *Publication* 113
Lowe C U May C D Stauffer H M and Neuhauser E D B (1950) *Amer J Dis Child* 79 91
Lundbaek K and Maaloe O (1947) *Acta physiol scand* 13 247
May C D and Lowe C U (1948) *J clin Invest* 27 226
Mead J F Bennett L R Decker A B and Schoenberg M D (1950) 536 *Atomic Energy Project Report* UCLA 88
Molander D W (1949) *Yale J Biol Med* 21 201
Munk I von and Rosenstein A (1891) *Virchows Arch* 123 230 484
Parsons L G (1932) *Amer J Dis Child* 43 1293
Perlman I Ruben S and Chaikoff I L (1938) *J biol Chem* 122 169
Raper H S (1913) *Ibid* 14 117
Schmidt Nielsen K (1946) *Acta physiol scand* 12 *Suppl* 37
Sinclair R G (1929) *J biol Chem* 82 117
— (1936) *Ibid* 115 211
Stetten de W Jun (1943) *Ibid* 147 327
Stillman N Entenman C Anderson E and Chaikoff, I L (1942) *Endocrinology* 31 481
Stryker W A (1941) *Arch Path* 31 670
Thompson M D (1948) 'The intraluminar phase of fat absorption in man *Ph D Thesis* University of Birmingham
Twort J M and Twort C C (1932) *Lancet* 2 448
Verkade P E (1948) *Arch sci phys* Proc Symposium des Lipides
Verzár F and Kuthy A von (1931) *Biochem Z* 230 451
— and Laszt L (1934) *Ibid* 270 35
— — (1935) *Ibid* 276 396
— and McDougall E J (1936) *Absorption from the Intestine* London Longmans Green
Vonk H F Engel C and Engel C (1938) *Biochem Z* 295 171
Williams T D (1949) *J Physiol* 107 30 P
Zilversmit D B Entenman C and Chaikoff I L (1948) *J biol Chem* 172 637

CHAPTER 20

STEATORRHOEA AND REGIONAL ILEITIS

W TREVOR COOKE

SECTION I

STEATORRHOEA

DEFINITION

THE term steatorrhoea was original y applied bv Kuntzmann in 1824 to th presence of fat visible in the faeces The use of the term has now become wider to signify the presence of excess fat in the faeces visible or otherwise and independent of frequency or abnormality of stool appearance The steatorrhoea syndrome includes many clinical pictures that are associated with fat absorption defects but with the increasing awareness of the frequency of steatorrhoea and the differing clinical entities encountered the syndrome is becoming ill-defined This criticism appli s similarly to the synonymous terms sprue syndrome and jejuno-ileal insufficiency For the present steatorrhoea signifies excess fat in the faeces Its demonstration indicates the failure of a physiological process but not that such dysfunction is necessarily the primary aetiological factor in anv particular patient It should therefore be assessed as any other laboratory finding as part of the clinical picture In this wav an attempt may be made to define differing syndromes having the common factor of steatorrhoea

DETECTION OF STEATORRHOEA

A normal individual on a mixed diet excretes 5–7 grams of fat per day Hence the consistent excretion of more than 10 grams a day is satisfactory evidence of the presence of a defect of fat absorption Many patients with steatorrhoea absorb between 75 and 85 per cent of the fat ingested in which case the estimation of the fat excreted without knowing the quantity ingested mav not clarify diagnosis The adoption of a diet containing 50 grams of fat is convenient both for diagnosis *and treatment (Cooke and others 1946) In collecting stools for examination* the use of markers is tedious and unsatisfactory An enema given at the b ginning and end of the collection period discarding the results of the first enema and retaining those of the second is more accurate The actual p riod over which stools should be collected varies with each patient When the stools passed are fluid or semi formed one three-day collection is usually adequate Should

there be any tendency to constipation then successive three day collections should be made

Such balances may be carried out in the general ward but unless care is taken errors in diet food intake and of faecal collection may occur Errors of intake commonly result in too little fat being taken rather than too much and rarely invalidate the finding of steatorrhoea though clearly insufficient intake may mask the diagnosis Faults in collection may be revealed sometimes by the dried weight of faeces which is normally 20–30 grams per day Should the dry weight be less than 15 grams using the 50 gram diet suggested the result should be discarded or confirmed by a further test Using such a balance technique 90 per cent has been set as the lowest limit of normal whilst results below 85 per cent absorption are abnormal When values between 85 and 90 per cent are obtained further tests should be made to decide whether or not the fat absorption is consistently at this level Patients suffering with pernicious anaemia primary and secondary iron deficiency anaemia pernicious anaemia of pregnancy gastric and duodenal ulcers amoebic and bacillary dysentery cirrhosis of liver and many cases of ulcerative colitis absorb fat normally While a balance technique is the only way of assessing accurately a quantitive absorption defect there are three less tedious methods which may be used as primary screening techniques

Macroscopic appearance of the faeces—The gross appearance of the stools is not a reliable guide to the presence or absence of excess fat While pale or aluminium coloured offensive stools usually contain an excessive amount of fat this is not invariably so normally coloured and formed stools also may contain abnormal quantities of fat

Microscopical examination—This may show actual fat globules which in the absence of administration of liquid paraffin are strong evidence as to the presence of steatorrhoea Excessive amounts of fatty acid crystals are found in a high percentage of patients with steatorrhoea 10–15 per cent of patients with idiopathic steatorrhoea however do not show an excess whilst others with no steatorrhoea may do so

The traditional method of examining for steatorrhoea is estimation of the percentage fat in the dried weight of a single sample of faeces The normal values for this test vary between 15 and 25 In practice however abnormal quantities of fat may frequently be present even though the percentage fat lies between these values If the percentage is above 30 steatorrhoea is probable for in 100 such examples on three day balances only 4 had normal fat absorption tests

Creatorrhoea—Early examination of the stools of any patient with loose motions will usually show incompletely digested meat fibres If on the other hand examination is deferred for 24 hours only those patients in whom there is no trypsin as for example certain cases of pancreatitis still show muscle fibres

CLINICAL CONDITIONS

The clinical conditions in which steatorrhoea occurs may be provisionally subdivided into those in which there are pathological or structural changes and those in which there are no constant changes which can be regarded as significant

Pathological changes

(i) Bowel wall and mesentery

1 Intestinal lipodystrophy 2 primary intestinal tuberculosis 3 infestations—Giardia lamblia 4 granulomatous jejuno ileitis ileocolitis regional ileitis 5 amyloid disease 6 scleroderma 7 neoplasm Hodgkin s disease

(ii) Pancreatic disorders

(iii) Liver disorders

1 Infective hepatitis 2 obstructive jaundice

Structural changes

(i) Total gastrectomy

(ii) Partial gastrectomy

(iii) Small intestinal resection

(iv) Pancreatectomy

(v) Short circuit operations

1 gastroenterostomy 2 ileotransverse colostomy and 3 entero enterostomy

(vi) Intestinal fistulae gastrocolic ileocolic

No constant pathological changes

(i) Coeliac disease Idiopathic steatorrhoea Non tropical sprue (ii) Tropical sprue—acute and chronic— parasprue

Conditions associated with jaundice whether due to obstruction or infection are not ordinarily included in the steatorrhoea syndrom and will not be discussed further Customary sequence of presentation of a syndrome in which the primary aetiological factors are as yet unknown is not possible so that the findings encountered in idiopathic steatorrhoea will first be described Though by designation it must be a diagnosis by exclusion it presents a series of clinical features not explained by any recognizable specific pathological changes while in other types of steatorrhoea with pathological or structural changes the complete syndrome is not necessarily present

IDIOPATHIC STEATORRHOEA

(*Synonyms* Non tropical sprue and Coeliac disease)

This is primarily a chronic condition irrespective of the duration of the presenting symptoms At least half the patients have histories suggestive of coeliac disease in childhood The majority present with symptoms between 35 and 55 year of age Even of patients treated in childhood for coeliac disease very few have troublesome symptoms between 20 and 35 years The incidence in the sexes is approximately equal The principal complaint in 45 per cent of patients is diarrhoea Others in approximately equal numbers complain of weakness loss of weight lassitude anaemia and glossitis even though diarrhoea may be present The remainder present with miscellaneous symptoms such as abdominal discomfort tetany and spontaneous fractures

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no organic cause for the obstruction The liability for such attacks diminishes with improvement in the patient s general condition Four cases including one with idiopathic steatorrhoea have been operated upon in this clinic for such obstructive symptoms and there are many similar observations in the literature

Appetite —This is usually well maintained In many cases it may be enormously increased so that the patient will complain of always feeling hungry Steatorrhoea is one of the few conditions in which bulimia and marked loss of weight co exist

Loss of weight —Almost invariable in untreated patients This may vary from a few lb to as much as 60 lb in 3 months In 75 patients with idiopathic steator rhoea the average loss was 21 lb Such weight losses are invariably accompanied by a loss of energy but not necessarily by frequent watery stools

Tetany —A history of tetany in a mild form will be elicited from practically every patient *This like the weight loss is not necessarily associated with diarrhoea* though if diarrhoea has been at all prominent tetany may be troublesome In rare cases tetany may persist for 2–3 days with severe pain and generalized muscle spasm leading to shock and coma Such states are usually associated with marked dehydration and hypokalaemia

Hypokalaemia —*In any diarrhoea there is an increased loss of electrolytes in the* stools In steatorrhoea the loss of potassium may be maintained even in the absence of loose stools so that 2–4 grams are lost daily In consequence most patients with the steatorrhoea syndrome tend to become deficient of electrolytes and water as the result of relatively minor disturbances

The importance of potassium lack in producing symptoms has only been recognized relatively recently In mild cases complaints of weakness and heavy limbs together with mental apathy and rapid weight loss may be noted The specificity of such complaints can be related to potassium deficiency by the finding of a low serum-potassium the removal of the symptoms and rapid replacement of weight on the administration of potassium While recent attacks of diarrhoea will tend to precipitate this syndrome mild manifestations may occur without obvious alteration in bowel habit It is possible that alterations in the distribution of the electrolytes is one of the chief fa tors causing the lassitude so often complained of by these patients

In severe cases weight loss may be more marked and rapid blood pressure low (around 70–80 systolic) reflexes may disappear and muscle weakness be profound Mental apathy and personality changes may be prominent In such cases the abdomen may b come distended simulating ileus and the associated vomiting causes further loss of potassium Replacement therapy can even in those most severely depleted and ill bring about a rapid recovery

If unrecognized the patient gradually passes into coma and dies becoming excessively dehydrated even in the absence of diarrhoea Perusal of the literature and of our own cases suggests that hypokalaemia is one of the common causes of death in this syndrome Recognition of the importance of potassium therapy has enabled us to restore to full working life a few patients when previous exp ri ence would have adjudged them too severely ill for recovery

Glossitis —This occurs at some time in nearly every case of idiopathic steator rhoea but there are no appearances specific to steatorrhoea All degrees of glossitis may be encountered either of an acute or chronic nature The lesions are usually

SYMPTOMS

Bowel habits.—One case in five has completely normal bowel habits. It must also be stressed that in only half of the patients with attacks of diarrhoea do such attacks lead to the seeking of medical advice. As Thaysen (1932) wrote: "Intestinal symptoms, especially diarrhoea, have persisted for years before this disease is diagnosed as non-tropical sprue. In such cases, where the patients have got accustomed to their diarrhoea and have lost interest in their disease, and where consulting physicians have not been sufficiently interested in the appearance of the stools as to examine them by inspection, it is not to be wondered that the disease is not diagnosed before the diarrhoea was complicated with a severe degree of anaemia, glossitis, or extreme debility." It is not, however, only those in whom the loose stools have been present for years that make no mention of them. Some patients are too occupied with their lassitude, glossitis and loss of weight to offer evidence of a recently developed attack of diarrhoea.

Attacks of normally coloured or pale, watery stools 2–4 times a year lasting from 2–14 days, later becoming more frequent, usually without any associated pain though sometimes accompanied by tenesmus, are the most common bowel disturbance. The onset of such attacks is variable, sometimes with gradual increasing looseness, at others explosive in its suddenness. As in most diarrhoeal conditions nocturnal attacks with actual incontinence are frequent. Often the attacks of loose motions are confined to the early morning, the remainder of the day being entirely undisturbed. The number of stools varies, though it is rarely more than 8 per day. On the other hand, the attacks may consist merely of the passage of 1–2 large, bulky, offensive, pale stools each 24 hours. In between the attacks the bowel habits of the majority become normal, but in occasional patients constipation may necessitate the use of purgatives.

Lassitude usually accompanies severe diarrhoea and anaemia. In idiopathic steatorrhoea, however, this symptom occurs even when anaemia is mild or non-existent and bowel actions uneventful. The symptom is such that patients express themselves as not knowing how to carry on owing to tiredness or ready to fall asleep at any excuse. Nevertheless, with few exceptions, they lead a full life with many outside interests, such as preaching, youth movements, theatre work, so that initiative at least appears to be unimpaired and mental drive only slightly so.

Abdominal pain and discomfort.—In the majority of patients abdominal symptoms are relatively mild. Disturbing flatulence or flatus troubles more than half the patients and nausea, usually associated with attacks of diarrhoea, occurs in approximately one-third of the patients. *Vomiting is not so common but it may occur* in some patients without warning so that pyloric stenosis is simulated, especially when gastric stasis is present on radiological examination. Most patients admit to *mild abdominal discomfort which*, if *related to meals*, may mimic peptic ulceration. Only in a few patients is distension sufficiently marked to cause complaint, though the abdomen tends to be more prominent than normal.

Severe abdominal pain is not common and should lead to a careful search for a more significant aetiology. There is one cause, however, which merits careful note. Patients with steatorrhoea are liable to attacks of gaseous distension. When this occurs in an elongated and possibly unduly large colon, or atonic small intestine, partial or complete volvulus can occur. Subsequent operation reveals

occasionally even oral pigmentation is present More commonly however the pigmentation affects the exposed surfaces and resembles pellagra In such cases exposure to sunlight leads to rapid pigmentation with a pavement type of epithelium Though bullous formation and subsequent epithelization as in fully developed pellagra has not been encountered in our patients the similarity of the distribution and type of skin lesions to mild pellagra may for convenience be termed pellagroid Indeed the presence of macrocytic anaemia and fatty diarrhoea in certain fully developed pellagrinous patients raises many fundamental questions of definition In addition to these two main types of pigmentation deeply pigmented patches may develop especially in areas where there has been any breakage of the epithelial surface or undue pressure

A low grade pyrexia is not infrequent and in occasional patients bouts of fever of 1–3 weeks may occur without obvious cause Physical examination of the chest usually fails to reveal any abnormality Examination of the heart however shows a higher incidence of rheumatic involvement (10 100) than might be expected in an unselected series of patients Blood pressure is low and a systolic pressure of 95 millimetres of mercury or less is encountered at some time irrespective of the nutritional state in more than one third of patients Hypertension on the other hand is rare In occasional cases the liver is enlarged and returns to normal size with improvement in the general condition The spleen is moderately enlarged in 10 per cent of patients Sigmoidoscopy often reveals a red velvety mucous membrane bleeding easily with minimal trauma while gastroscopy may show atrophy of the gastric mucosa

Few defects are found on neurological examination Absent reflexes occur chiefly in association with hypokalaemia rather than as manifestations of a true peripheral neuritis Nevertheless findings identical with subacute combined degeneration do occasionally occur they have been encountered in only 2 of 127 adults with idiopathic steatorrhoea Both were completely bedridden but with treatment both made a complete recovery with reversion to flexor plantar responses

Radiological examination of the skeleton usually reveals minimal decalcification of the spine Occasional patients show a generalized rarefaction of bones with spontaneous fractures which may be single or multiple Even when they are extensive as in one patient with fractures in 12 ribs both scapulae and the pubis they are comparatively painless and may be diagnosed as rheumatism Rapid healing takes place with administration of vitamin D The nature of the bone changes has not been completely established Though osteomalacia is the lesion usually assigned in many cases actual osteoporosis is present Both factors are probably concerned in varying degrees in different patients

Radiological examination of the small intestine is considered in Chapter 21 That of the colon has been described by Bennett Hunter and Vaughan (1932) Though no abnormality is usually found with a barium enema in some cases definite elongation and redundancy of the colon is present whilst in other cases the colon may approach the size of a primary megacolon

Haematological examination in idiopathic steatorrhoea almost always shows some abnormality (Cooke and others 1948) In cases originally presenting a normal blood picture subsequent examinations will show the pattern variation to be expected If in the absence of specific treatment the blood count is persistently

confined to the mouth and tongue but may occasionally extend down the pharynx and oesophagus with resultant dysphagia and cardiospasm Perianal excoriation and vaginitis can also prove troublesome though reacting relatively quickly to vitamin therapy Exacerbation of these vitamin deficiencies is frequently initiated by the relapse of diarrhoea or anaemia In some the recurrence of glossitis is always related to menstruation Nevertheless in some patients glossitis may have no obvious precipitating factors

Skin rashes —Approximately one in five patients seek medical advice on account of skin rashes The principal lesion is seborrhoeic dermatitis a desquamating type of rash affecting the hands forearms legs and occasionally the face Of particular interest is the relatively high incidence of lesions simulating psoriasis often appearing only when the patient is markedly debilitated

Haemorrhagic manifestations —Extensive subcutaneous haemorrhages may be found in any patient seriously ill with steatorrhoea but severe haemorrhagic manifestations may also be encountered in patients who are otherwise apparently well Profuse haematuria melaena purpura and joint swellings as well as sub cutaneous haemorrhages may occur, and unless the possibility of steatorrhoea be considered the complete diagnosis will be missed These disorders have been attributed to vitamin K deficiency but further work is necessary before a satisfac tory explanation can be advanced for this group of haemorrhagic disturbances

Sex characteristics —Menstrual irregularities are not especially common In the majority of patients menarche and menopause occur at the normal times and the menstrual cycle is without diagnostic incident Fertility is lowered to some extent but normal pregnancy may occur even in cases where mild macrocytic anaemia and slight fat absorption defects are still present Pregnancy itself appears to have no ill effect Male potency is maintained even in the presence of moderately severe constitutional upsets though a small number of patients are impotent Hair growth is retarded in most of the men so that shaving is necessary only 2–3 times a week

EXAMINATION

The majority of men and women with idiopathic steatorrhoea are of average height and weight and the occurrence of coeliac disease in childhood plays little part in the ultimate adult height of the patient Thus one patient who spent 7 of his first 14 years of life in hospital with coeliac disease is now at age 21 5 ft 7 in and 10 stone just above the average height of the age group of his district Idiopathic steatorrhoea in tall patients is rare

Facial appearance differs between males and females the males presenting a broad head and narrow chin giving a triangular appearance to frontal view females having a rounded face with prominent zygomatic arches as was pointed out by Bennett Hunter and Vaughan (1932) The hair is usually fine and straight Coarse wavy hair dark or black does not appear but premature greying is common and is often claimed as a familial characteristic by the patient Finger clubbing occurs in 15 per cent of patients and disappears with improvement in general condition

Though a few patients maintain a pink and white complexion pigmentation occurs in the majority This may be generalized and simulate Addison s disease

though in a few the ratio of free to ester cholesterol is reversed Cephalin cholesterol colloidal gold and thymol turbidity tests are collectively abnormal only in seriously ill patients In ambulant patients one of the tests may sometimes be found abnormal Serum bilirubin is rarely raised above 2–3 milligrams per 100 millilitres In the majority of patients irrespective of their clinical state the values are within the normal range The alkaline phosphatase may be raised and usually indicates bone disorder rather than liver dysfunction

Amino aciduria

Many of these patients show an increased excretion of amino acids as detected by chromatography (Bickel 1951) The significance of this finding is as yet conjectural It may indicate a general liver disorder or alternatively some intrinsic metabolic disorder leading to the deficiency of one or more of the essential amino acids and hence to the excret on of the others

Glucose tolerance tests

The finding of a flat glucose tolerance test (usually defined as a rise of less than 40 milligrams per 100 millilitres during the test) has traditionally been accepted as one of the diagnostic criteria The average rise in 70 such tests was 47 milligrams and the maximum was usually obtained at the end of one hour as opposed to 30 minutes in normal individuals The tests however vary from time to time in the same individual and the occurrence of pyrexia in a patient for example may enable a perfectly normal tolerance curve to be obtained Flat curves are usually interpreted as being due to failure of absorption but the evidence on which this is based is by no means secure In view of the part played by the liver and the adrenals in carbohydrate metabolism it is perhaps unwise to speculate further on the significance of the lowered curve that is so frequently found

Iron tolerance tests

Following an oral test dose of ferrous sulphate 10 grains both flat and normal serum iron curves may be obtained in patients with idiopathic steatorrhoea without any correlation with the clinical state and the degree of steatorrhoea Intravenous loading tests also show much variation Thus in some when serum iron is determined five minutes after injection more iron than expected has already disappeared from the serum In others though the five minute reading may be as calculated the fall in serum iron may be more rapid than normal The findings are essentially comparable to those in infection and certain macrocytic anaemias Poor iron absorption has been usually considered the cause of both the hypochromic anaemia of idiopathic steatorrhoea and the low iron absorption curves As with glucose metabolism this view is not completely satisfactory

Ascorbic acid saturation tests

Many patients are difficult to saturate with ascorbic acid and yet clinical signs of scurvy are rare neither is the plasma ascorbic acid low The administration of ascorbic acid by intramuscular or intravenous routes appears to make little difference so that mal absorption does not play any major part The cause of this difficulty in saturating the patients is not yet apparent but the possibility of a defect in utilization must be considered

normal idiopathic steatorrhoea is unlikely When first seen two thirds of the patients have macrocytosis demonstrable by increased mean cell volume or by a Price Jones curve In a few cases the peripheral blood may be indistinguishable from that of pernicious anaemia In general microcytosis is not seen even in the severe hypochromic anaemia of steatorrhoea Commonly there is a mixture of large and normal sized cells with great variation in depth of staining termed dimorphic Following treatment every case shows macrocytosis at some stage and those initially macrocytic frequently show a temporary phase of normocytic cells hypochromia and low colour index The macrocytes in idiopathic steatorrhoea are not necessarily larger in volume for the cells are thinner than normal resembling in every way those seen in liver dysfunction from any cause Fragility to hypertonic saline is usually decreased Leucopenia is the common finding and platelets are usually present in normal numbers Sternal puncture will reveal megaloblasts in a third of the cases whilst an approximately equal number will show cells described elsewhere as atypical normoblasts

BIOCHEMICAL FINDINGS AND THEIR SIGNIFICANCE

The composition of the plasma in idiopathic steatorrhoea is dependent principally *upon the state of hydration and nutrition of the patient and not upon the presence* of steatorrhoea Thus great variation in the values for sodium potassium calcium chloride and phosphate may be noted Significant findings when they occur are low sodium 110 milliequivalents or less low potassium less than 3 5 milliequivalents and low calcium which may be as low as 6 milligrams per 100 millilitres Low values for any of these cations are indications for their replacement The lack of sodium and potassium is almost entirely due to the excessive losses in faeces and urine irrespective of whether there is diarrhoea or not The tendency to low calcium has usually been attributed to the immobilization of calcium by the formation of insoluble calcium soaps It has however been pointed out that the calcium lost is often in excess of that which can be attributed to soap formation (Basset and others 1939) Though there is as yet no laboratory proof much of the calcium loss may well be a compensatory mechanism for conserving the more essential bases sodium and potassium a substitution seen in renal acidosis when the essential reserves are threatened In practice deficiencies of any one base should lead to consideration of the state of the other two

Serum proteins

In a series of 90 cases of idiopathic steatorrhoea only 5 patients have had total serum proteins of 5 milligrams per 100 millilitres or less and only 7 serum albumin less than 3 5 milligrams Low serum proteins indicate a more serious prognosis and are frequently difficult to correct but even in long standing cases of idiopathic steatorrhoea cure and return to normal health can be procured

Liver function tests

Low total plasma cholesterol is found in many cases but the finding is more closely correlated with the degree of anaemia than the severity of the steatorrhoea In the majority of patients free and ester cholesterol lie within the normal range

the clinic In those patients in whom intestinal disturbances have not been prominent refractory macrocytic anaemia has frequently been diagnosed

In the second group the chief conditions are refractory macrocytic anaemia achrestic anaemia pernicious anaemia cirrhosis of liver ulcerative colitis and Addison s disease In a few cases of ulcerative colitis abnormal fat balances will be found In 20 so far investigated 4 have shown a mild defect recovering as the condition improves Since in many cases of ulcerative colitis the ileum is involved these abnormal balances may signify such involvement

The third group contains all the conditions in which steatorrhoea is usually found and the separate entities therefore will be discussed Regional enteritis will be treated in a separate section

Intestinal lipodystrophy of Whipple

In 1907 Whipple described a patient suffering with mild joint swelling diarrhoea anaemia and loss of weight At autopsy pathological changes were demonstrated in the intestinal wall and in the enlarged mesenteric glands consisting principally of plasma cells giant cells and fat engorgement Since then more than 40 similar cases have been described in which varying changes in the bowel wall and mesenteric glands have been noted (Hendrix and others 1950 Plummer and others 1950) The diagnosis in each case has been based upon autopsy or surgical biopsy

The principal clinical symptoms are essentially those of idiopathic steatorrhoea Stress has however been laid on the frequent occurrence of pericarditis and endocarditis Nevertheless the incidence of definite long standing rheumatic infection is no higher than that which has been noted in our series of idiopathic steatorrhoea Many of the patients have been operated upon for apparent intestinal obstruction (*vide supra*) when the enlarged glands have been noted In one series six such cases have been diagnosed either by autopsy or operation The conclusion has been reached that intestinal lipodystrophy is one form of idiopathic steatorrhoea and that the changes noted in the mesenteric glands are probably variations of the normal reaction occurring in the mesenteric glands to stimuli of varied type and intensity If such is the case then many cases of idiopathic steatorrhoea will fall into this group whilst in some patients such histological changes will be found without any obvious association with the steatorrhoea syndrome (Pemberton and others 1947 Stryker 1941)

Tuberculous mesenteric glands

Traditionally these have been thought to be associated with steatorrhoea but this view is probably erroneous Involvement of the mesenteric glands by a tuberculous process is rarely generalized and should steatorrhoea be demonstrated to be associated with tuberculous glands then involvement of the intestinal wall will be demonstrated Primary intestinal tuberculosis however *is one of the rare* causes of the steatorrhoea syndrome mimicking in every way except in the downhill course the picture of idiopathic steatorrhoea

Scleroderma

The importance of involvement of the bowel wall as a factor producing steatorrhoea is suggested by its occurrence in scleroderma In 5 such patients

Fractional test meals

Approximately 20 per cent of patients have a histamine fast achlorhydria Rather more have only a trace of acid whilst the remainder have normal quantities With improvement in their clinical state some patients with a histamine fast achlorhydria originally may again produce free hydrochloric acid in the stomach contents

Duodenal intubation

Analysis of the duodenal contents have shown that trypsin amylase and lipase are present in normal quantities (Comfort and others 1949) It is however difficult to explain the cases in which there is a deficiency of enzymes whether it is a temporary phenomenon due to the intubation the patient s condition or whether it is a manifestation of chronic pancreatic disorder Unfortunately both the technique of obtaining reliable samples and the methods of analysis are somewhat unsatisfactory Since in any event only a few of the possible enzymes can be studied the procedure remains a research procedure

To sum up the information to be gained from biochemical analysis there is only one essential abnormality that is the faecal fat content The other estimations serve to fill in the picture of the various metabolic disorders accompanying idiopathic steatorrhoea

FAMILIAL INCIDENCE

Thaysen (1932) suggested that there was no familial incidence to be found but in later reports he described such cases (1935) More recently Davidson Girdwood and Innes (1947) and Davidson and Fountain (1950) have put forward evidence suggesting an increased familial incidence in coeliac disease There is now a large number of reports of single families in which more than one member is affected with the steatorrhoea syndrome In this clinic out of 94 families at present available 10 have so far been shown to have more than 1 member affected these 10 families producing 38 cases It is probable that the incidence is higher since the frequency of such disorders as colitis anaemia and sore tongue in relatives not yet examined is high This high familial incidence may provide a significant clue to the aetiology of idiopathic steatorrhoea

DIFFERENTIAL DIAGNOSIS

The conditions from which idiopathic steatorrhoea must be differentiated may be classed into three groups

(1) Certain ill defined conditions in which further investigation may show the presence and probable aetiological relationship of steatorrhoea
(2) *Conditions* with similar symptoms in which steatorrhoea is not usually present
(3) Conditions in which steatorrhoea is usually present

In the first group may be placed tuberculous bowels so frequently diagnosed in childhood *many cases of tabes mesenterica* and occasional cases of tuberculous peritonitis in adults Chronic enteritis and colitis are two further syndromes which in the absence of gross pus and blood and pathogenic bacteria will frequently be shown to be cases *with steatorrhoea* Lienteric diarrhoea may also mask the correct diagnosis of steatorrhoea in some cases whilst functional or nervous diarrhoea has appeared in the previous histories of many patients in

glossitis anaemia and upsets of protein and electrolyte metabolism In this group the upsets of protein and electrolytes are in general more marked than in idiopathic steatorrhoea Such conditions may follow disease or surgical intervention

Patients with gastrocolic gastro jejunocolic and duodenocolic fistulae develop a marked steatorrhoea and usually a fall in serum protein with associated oedema Hypokalaemia is common Since the deterioration in such cases is usually rapid macrocytic anaemia is rarely seen While diarrhoea is almost invariable rare patients will have no upset of bowel habit Such rapid deterioration will sometimes be seen as the result of gastrectomy when the ileum has been used for anastomosis in error

Enteroenterostomosis and ileocolostomies result in less acute and severe manifestations Low serum proteins are frequently found in association with steatorrhoea of varying degrees and a macrocytic anaemia Thus symptoms following short-circuit operations for intestinal obstruction as for example occasionally follows appendicectomy may not appear for some years Restoration of the bowel continuity or excision of the by passed area will usually result in the complete restoration to health Extensive resection of bowel which was previously healthy does not necessarily cause any serious impairment of absorptive powers but in conditions such as regional ileitis where there is always doubt as to the condition of the rest of the bowel inferences as to its powers of absorption are not justified

Operation upon the stomach

Most operations upon the stomach give rise to some upset of fat absorption (Woolager and others 1946) The majority of patients suffer no inconvenience but a minority develop the full steatorrhoea syndrome The reasons for the interference are as yet not clear and any hypothesis as to the causes can only be speculative The steatorrhoea following total gastrectomy is usually gross and the fully developed steatorrhoea syndrome is frequently seen in such cases as survive long enough For a short period after partial gastrectomy when solid food is being taken again a fatty diarrhoea may be encountered In approximately 2 per cent of gastrectomies a troublesome fatty diarrhoea with lassitude and persistent low weight continues In such cases a mild macrocytic anaemia may develop and later some degree of iron deficiency may be superimposed Nearly all the cases may be controlled by a high protein low fat diet and energy and weight restored

Tropical sprue

By custom patients developing the steatorrhoea syndrome in a tropical country have been designated as suffering with tropical sprue Twenty five patients suffering with persistent symptoms more than 3 years after their original attack have been studied in this clinic and no essential difference between this group and the group designated idiopathic steatorrhoea has so far been detected This does not imply that the acute sprue syndrome is brought about by the same factor in every patient but merely that if persisting into a chronic state the clinical picture becomes indistinguishable in every respect save history from idiopathic steatorrhoea

2 presented on account of diarrhoea which was fatty on investigation and in all steatorrhoea of various degrees was present In those cases with marked sclerodermatous involvement of the intestine the radiological picture appears characteristic with greatly distended small intestine poor motility and a grossly dilated colon

Primary or secondary amyloid disease

Primary or secondary amyloid disease of the intestinal tract has been reported In such cases only autopsy examination has enabled the diagnosis to be made though the presence of lesions elsewhere conducive to the development of amyloidosis should lead to consideration of steatorrhoea in any diarrhoea that may occur

Granulomatous jejuno ileitis

An increasing number of cases on both radiological and autopsy findings has been reported under a variety of terms The clinical picture is that of a patient severely ill with the steatorrhoea syndrome whilst pathologically the intestinal wall tends to be oedematous with infiltration of plasma and giant cells When complete resolution occurs the distinction from idiopathic steatorrhoea may well be impossible If on the other hand histological material is available the distinction from some cases of regional ileiti or Whipple s disease may be equally difficult

Pancreatic disorders

The functions of the pancreas still remain obscure so that complete assessment of its role in the production of any of the clinical entities considered under the steatorrhoea syndrome is not yet possible The presence of steatorrhoea and creatorrhoea is no longer essential for the diagnosis of pancreatic disease Abundant evidence is available to show that neither is present in many such cases even with pancreatic lithiasis

Clinically the occurrence of long standing fatty stools without any associated weight loss glossitis or anaemia is suggestive evidence of a pancreatic defect Such clinical inference is often supported by a marked improvement in the bowel symptoms and steatorrhoea following the administration of a potent pancreatic extract While iron deficiency anaemia has occurred in many of the cases macrocytic anaemia has been rare so that its occurrence has led to consideration of other possible factors Experimentally certain functions of the pancreas are important in protecting the liver so that it is not surprising that a small number of patients with proved pancreatic disorder do present with liver disorders hepatomegaly low serum proteins and a macrocytic anaemia Clinically however it is difficult to assess whether pancreatic dysfunction or cirrhosis of the liver appeared first Certainly in such entities as kwashiorkor (Editorial 1949) liver dysfunction appears to precede the pancreatic fibrosis

Intestinal fistulae

By passing of any portion of the small intestine without exclusion of the by passed segment gives rise to varying degrees of steatorrhoea loss of weight

varying from a mild to severe steatosis. Actual cirrhosis occurs in some long standing cases, the histology resembling that of the nutritional type.

Changes occurring in other organs are not remarkable. Aplasia of the bone marrow does not occur. Osteoporosis and osteomalacia have been demonstrated.

Treatment

The treatment of the steatorrhoea syndrome is empirical and there is much justification for repeating Gee's statement (1888): "If the patient can be cured at all, it must be by means of diet." High protein and low fat diets are still the foundation of any modern treatment, usually 100–120 grams protein and approximately 50 grams of fat per day. Such a high protein intake can be attained both by extra meat and by dried milk products. In general, fats derived from milk are well tolerated. Butter, even to excess, can usually be taken without upset. In adults, cheese and milk rarely cause any disturbance, though children usually require the milk to be skimmed. On the other hand, fried foods such as fish and chips, fried bread and dripping should be excluded. Meat fats, especially mutton and pork, and any fat subjected to repeated heating, such as in stews and the deep frying pan, may seriously aggravate the steatorrhoea. Cooking fats vary greatly in their manufacture and digestibility but any may be used in the making of pastry and fancy cakes. Many patients are quite unable to tolerate such pastry though well able to eat home made varieties. Though certain starches and flours upset coeliac patients, there is no evidence at present as to their ill effects in adults.

Clinical observation is the only way of assessing the effect of high protein low fat diets in a condition subject to such spontaneous variation. Careful adherence to such diets gives the best results. For example, a farmer was treated for colitis for 3 years with a high calorie, low residue diet containing a large amount of fat, with increasing loss of weight and energy and eventual inability to work owing to weakness. With the institution of a high protein, low fat diet and iron therapy for his anaemia, he was taking his full share of heavy work within 9 months and has remained well and symptom free for the past 3 years.

In addition to dietetic measures, most patients with idiopathic steatorrhoea derive great benefit from a period of bed rest. Such measures alone are often sufficient to control the relaxed stools. It is, of course, difficult to dissociate rest and dietetic effects but some patients do not seem to improve until a remission is initiated by a period of bed rest.

The treatment of anaemia in idiopathic steatorrhoea is essentially individual and in some patients it must be recognized that none of the haematinics at present available will have any effect. Crude liver preparations have enjoyed a reputation in the steatorrhoea syndrome but even with large daily doses the results in general have been disappointing. In no patient has there been evidence of improvement in fat absorption attributable to liver therapy and in only a few has the initial haematological response been comparable to that seen in pernicious anaemia. As has frequently been pointed out, it is difficult to restore the blood to normal with liver injections alone. Purified liver extracts rarely give any response.

While some indication as to treatment may be obtained from examination of the peripheral blood films, sternal puncture may reveal the presence of megaloblasts. In such cases folic acid is most likely to give a response. The daily

Nutritional macrocytic anaemia

Darby and Jones (1950) define nutritional macrocytic anaemia as a syndrome of macrocytic anaemia with megaloblastic bone marrow inconstant glossitis diarrhoea and absorption defects Neurological involvement is rare Castle s intrinsic factor is present It seems evident that many of the patients classed as idiopathic steatorrhoea in this clinic would be diagnosed by some as nutritional macrocytic anaemia This confusion again focuses attention on the difficulty of accurate classification and definition in the absence of complete knowledge of all factors concerned

Pathology

Thaysen (1932) concluded that There were no pathological features of a primary nature and that any findings of a definitive nature were secondary His views have influenced opinion so strongly that it has become axiomatic that idiopathic steatorrhoea should have no pathological features Consequently the finding of any histological abnormality in the intestinal tract or mesentery automatically has excluded such a diagnosis

Information as to the possible changes in the intestinal tract has been limited by the difficulties in obtaining satisfactory post mortem material unspoilt by autolysis Though it is probable that changes will be demonstrated eventually the defects of present techniques make it difficult to evaluate the significance of those findings that have been reported Enteritis characterized by oedema and mucus formation superficial ulceration cellular infiltration intestinal atrophy and degeneration of Auerbach and Meissner s plexuses have been describ d but with the exception of the neural degeneration have been ascribed to terminal processes Schein (1947) has described changes in the tips of the villi which he regards as specific for certain types of steatorrhoea but more evidence is needed before the significance of his findings can be assessed

Changes also occur with great frequency in the mesenteric glands Various degrees of enlargement are the rule rather than the exception The most marked cases are those reported in Whipple s disease This group is however a selected series in that the diagnosis depends in essence upon the finding of enlarged glands with certain histological features Examination of the mesenteric glands of patients with idiopathic steatorrhoea suggests that the pattern seen in Whipple s disease may as stated earlier be due to a variation in either the duration or intensity of the primary irritant Furthermore examination of glands from patients without steatorrhoea will reveal glands essentially similar to those reported as Whipple s Occasionally degeneration of the gland forms a white caseous material which may be mistaken for tuberculous caseation Sufficient evidence has been collected now to suggest that generalized enlargement of the mesenteric glands are non tuberculous in most cases Thus whilst in any particular patient with steatorrho a the enlarged mesenteric glands may bear a close aetiological relationship to mal absorption of fat the enlargement and histological changes cannot b regarded as specific for the steatorrhoea syndrome alone

Many of th reported autopsies reveal some degree of fibrosis of the pancreas but whether this represents a primary disorder or merely the result of a long standing nutritional disorder is difficult to state The liver often shows changes

been exceptional to achieve this without at least 12 months treatment The remainder have varying degrees of anaemia some even after 8 years treatment with trials of all available haematinics

GENERAL DISCUSSION ON AETIOLOGY

As yet there is no adequate aetiological explanation for idiopathic steatorrhoea Since the presence of excess fat in the faeces is an essential requirement for the diagnosis it is not surprising that the failure of absorption has been blamed for all the symptoms that arise Thus the low glucose tolerance and vitamin A curves the vitamin deficiencies and the anaemias have all been attributed to this cause (Snell 1939 Hurst 1942) In putting such an explanation forward there is little to indicate how failure of absorption has arisen Thaysen (1932) discussed three possible theories infection avitaminosis and constitution In tropical sprue previous attacks of dysentery have been blamed and in non tropical sprue similar types of infection have been incriminated The theory may be revived in considering the aetiology of the steatorrhoea of gastrocolic fistulae blind loops or entero enterostomies when infection of the upper gut by inhabitants from lower down may well play a significant part Avitaminosis attracted support but Thaysen in 1932 was unable to find much evidence in support of it Experimentally it is possible to produce by various vitamin deficiencies the anaemia and fatty diarrhoea Such experiments however produce effects on other systems within the body and so set in train many other metabolic changes In man pellagra produces symptoms similar to those of some patients with idiopathic steatorrhoea but whereas the diet in the pellagrinous patient is generally deficient the diet of the average patient with steatorrhoea is good Frazer (1950) has considered a combination of both the infection and avitaminosis suggesting that the altered flora in the intestinal tract enters into competition with the host for the vitamins so producing many of the secondary manifestations The third theory which Thaysen considered was the constitutional theory When the constitution theory seems the most easy to understand with our present knowledge of the question it is only because it works with such a vague and obscure conception as individual constitution a conception we have to accept as reality though its details are so obscure that the whole constitution theory does not really help us one step nearer to actual understanding of the aetiology of sprue This theory still holds many attractions since there is much more known about possible defects of enzyme systems and other metabolic processes In seeking for such defects Verzar (1935) suggested that the failure of absorption was in large measure due to failure of phosphorylation in the intestinal cell brought about by failure of the adrenals This view has not been generally accepted since in the presence of adequate sodium short chained fatty acids are absorbed by adrenalectomized animals at a normal rate whilst that of long-chained fatty acids are seriously impaired Since however it is the long-chained fatty acids where absorption is principally impaired in idiopathic steatorrhoea it is possible that failure of production or utilization of one of the adrenal corticoids may be one of the factors producing this syndrome

From the clinical observation of large numbers of patients with idiopathic

requirements however may be as high as 15–20 milligrams daily Even though a good initial response is obtained, the likelihood of obtaining normal values with large doses of folic acid is problematical Again as with liver no effect has been noted on the fat absorption In a few cases glossitis has been improved

Vitamin B_{12} will also give good results In those that do respond initially the results have seemed rather better than those given by folic acid both on the constitutional symptoms the glossitis and the anaemia The patients however who respond are not so common as those who respond to folic acid neither is the presence of megaloblasts an indication that the anaemia will react to vitamin B_{12}

The need for iron administration is revealed by the mean corpuscular haemoglobin concentration falling below 28 per cent The peripheral blood picture may still be macrocytic or have changes to normocytic in each case accompanied by marked hypochromia Often this may be remedied by the administration of oral iron In some patients however oral therapy has no effect or is not tolerated In such cases the intravenous administration of iron will result in curing the iron deficiency and a reversion to macrocytosis (Hawkins Peeney and Cooke 1950)

Since none of the therapies directed to control of anaemia can be regarded as specific for the disorder and since many patients may have a mild anaemia for years without treatment the question as to maintenance treatment will depend upon the individual patient It is not essential in every case though some will require continuous treatment for many years

Glossitis in the majority of cases is well controlled with nicotinic acid 300–400 milligrams daily and riboflavine 5–10 milligrams daily In a few cases intensive injection of liver extract vitamin B_{12} pyridoxine or pantothenic acid may be necessary

Lassitude in some patients appears to be the result of hypokalaemia In such patients the administration of meat extracts or potassium salts has good effects whilst in those patients severely dehydrated parenteral administration of suitable mixtures of electrolytes is indicated In view of the frequency of hypokalaemia in these episodes the administration of DOCA or Eucortone on the basis of mis diagnosis or similarity to Addison s disease may precipitate serious results by increasing the excretion of potassium

PROGNOSIS

Prognosis in idiopathic steatorrhoea depends upon adequate medical supervision and treatment Of 100 cases analysed in this respect 70 can be regarded a having satisfactory health with regard to ability to carry out their work efficiently Sixteen on the other hand enjoy only moderate health limited by lassitude and periods of more marked incapacity Only 1 of the 6 males over 65 years of age has had to give up work The others still carry on full time work though with more sick leave than average and not in such strenuous occupations as they had previously Fourteen patients had died of which 10 appeared due to water and electrolyte disturbances principally hypokalaemia With recognition of this disturbance some at least of these patients should have survived Of the surviving members of the group 32 have now normal blood counts though it has

Personal observations in this chapter have been based upon experiences over the past 10 years of 300 patients with steatorrhoea or allied disorders including 127 diagnosed as idiopathic steatorrhoea 37 as tropical sprue 37 as pancreatitis 39 as regional ileitis and 14 as gastrocolic fistulae

REFERENCES

Bassett S H Keutmann F H Hyde H Z and Van Alstine H E (1939) *J clin Invest* 18 121

Bennett T I Hunter D and Vaughan J M (1932) *Quart J Med* 1 603

Bickel F (1951) Personal communication

Comfort M W Dornberger G R Wollaeger E E and Power M H (1949) *Gastroenterology* 13 135

Cooke W T Elkes J J Frazer A C Parkes J Peeney A L P Sammons H G and Garfield Thomas (1946) *Quart J Med* 159 141

— Frazer A C Peeney A L P Sammons H G and Thompson M D (1948) *Ibid* 41 9

Darby W J and Jones E (1950) *Clinical Nutrition* New York Paul B Hoeber

Davidson L S P Girdwood R H and Innes E M (1947) *Lancet* 1 511

— and Fountain J R (1950) *Brit med J* 1 1157

Editorial Kwashiorkor (1949) *Lancet* 1 188

Frazer A C (1950) In *Modern Trends in Paediatrics* London Butterworth

Gee S (1888) *St Bart s Hosp Rep* 24 17

Hawkins C I Peeney A L P and Cooke W T (1950) *Lancet* 2 387

Hendrix J P Black Schaffer B Withers R W and Handler P (1950) *Arch intern Med* 85 91

Hurst A (1942) *Guy s Hosp Rep* 91 1

Kuntzmann (18 4) *Journal der Pract Heilkunde* 59 3 Stuck 45

Pemberton J d J Comfort M W Fair E and Zaslow J (1947) *Surg Gynec Obstet* 85 85

Plummer K Russi S and Harris W H (1950) *Arch intern Med* 86 280

Schein J (1947) *Gastroenterology* 8 438

Snell A M (1939) *Arch intern Med* 12 1632

Stefanini M (1948) *Medicine* 27 379

Stryker W A (1941) *Arch Path* 31 670

Thaysen H Th E (1932) *Non tropical Sprue* London Humphrey Milford

— (1935) *Quart J Med* 28 359

Verzár F and Laszt L (1935) *Biochem Z* 276 396

Waterlow J C (1948) *Spec Rep med Res Council Lond* 263

Whipple G H (1907) *Johns Hopk Hosp Bull* 18 382

Wollaeger E E Comfort M W Weir J F and Osterberg A E (1946) *Gastroenterology* 6 94

steatorrhoea the conclusion seems unavoidable that there is a constitutional factor operating in these patients and that this may be inherited or acquired As Davidson and his colleagues (1947) have pointed out the high familial incidence in the absence of other obvious factors to give such a high incidence is strong evidence of some inherent metabolic defect The long history of intermittent symptoms the remission at the onset of puberty the independence of the vitamin defects and anaemia from the alterations in severity of steatorrhoea all point more to a constitutional defect rather than a primary intestinal disorder A striking feature in many patients is the relative mildness of the steatorrhoea in contrast to the refractoriness of the anaemia and glossitis From the occurrence in a family of some patients with typical idiopathic steatorrhoea along with others in whom fat absorption is consistently normal but in whom the macrocytic anaemia is of the refractory type steatorrhoea appears to be merely one of the many manifestations of this constitutional upset though for the moment it must remain as our only definite criteria of diagnosis The results of ascorbic acid glucose and iron tolerance tests all present features explicable on the basis of mal utilization in addition to the possibility of mal absorption

Certain more acute conditions may eventually provide the key to the problem as to whether a primary lack in the digestive process of the intestinal tract gives rise through mal absorption to constitutional upsets or *vice versa* On the reinstitution of feeding following starvation a phase of steatorrhoea and macro cytic anaemia frequently occurs In Africa kwashiorkor (Editorial 1949) offers many similarities to idiopathic steatorrhoea and has been attributed to lack of protein In the West Indies and West Africa protein lack has been associated with deficiencies of certain essential enzymes in the fatty liver syndrome (Waterlow 1948) *Stefanini (1948) has correlated a higher incidence of sprue with a lower* intake of protein A common factor in all these syndromes is protein lack In idiopathic steatorrhoea there is usually no dietary lack but increased intake *appears to produce most consistently the best results It is therefore tempting to* suggest that upsets in the intrinsic metabolism of protein may prove to be as important in this syndrome as the more obvious fat defect

In gastrocolic *fistulae on the other hand the cause of the absorptive defects* must be associated with the soiling of the small intestinal contents by those of the colon If this is prevented as by a colostomy proximal to the site of fistula the *steatorrhoea will disappear and the patient s condition improve considerably* The actual mode of interference is not clear whether by competitive bacterial utilization of vitamins and enzymes or by upset of the optimum chemical environ ment in the *lumen for normal intestinal digestion Similarly in the entero* enterostomies the same condition may hold good and in both types of disorder reconstruction of the alimentary tract leads to restoration of normal function The anaemias *vitamin deficiencies and other evidences of possible liver dysfunction* would be explicable by the resulting difficulty in dealing with the abnormal products of digestion The difference between the two groups clinically will not *be great In idiopathic* steatorrhoea the cycle of events will be initiated by the intrinsic defect whilst in the structural defects the process will be initiated by the intestinal changes and the one when initiated will set in motion the other

The mesenteric lymph glands are usually enlarged though this is not invariable Histological examination shows all variations of reaction oedema non specific inflammation necrosis giant cell formation and fibrosis (Crohn 1949 Hadfield 1939 Warren and Sommers 1948 Schepers 1945)

To sum up regional ileitis though clinically a distinct entity has no pathognomonic histological features

AETIOLOGY

In spite of many attempts to isolate a specific bacterial agent (Pumphrey 1938) none has been successful Viruses animal parasites bacterial toxins foreign bodies impairment of blood supply appendiceal inflammation neurotropic disturbances hormone imbalance and vitamin deficiencies have all been suggested On the basis of the similarity of the pathological findings some workers consider that the tubercle bacillus is the cause of the disease (Bockus 1945) and the possibility of sarcoid has also been put forward (Hadfield 1939 Crohn 1939)

Experimentally Reichert and Mathes (1936) produced intestinal oedema and fibrosis by the injecting of the lymphatics of the small bowel mesentery of dogs with finely divided sand and other sclerosing solutions In humans however obstruction of the lymphatics frequently cannot be demonstrated More convincing are the results of Chess and others (1950) who produced in dogs changes indistinguishable from regional ileitis following feeding fine sand These changes were found principally in the terminal ileum though the whole small intestine was involved with the exception of the duodenum In 2 of their 15 dogs granulomas also occurred in the liver If in addition to feeding sand an inj ction of viable bacteria was made an ulcerating enteritis was superimposed upon the reactive picture already produced They drew attention to the possible harmful ingestion of certain types of tooth paste and certain industrial occupations as possible causes of the condition in man These experiments appear highly significant pointing to a non infective or possibly absorptive defect as one of the causes of regional ileitis A number of workers have drawn attention to a relatively high incidence of such substances as talc enmeshed in the pathological reaction (Lightman and others 1946 Warren and Sommers 1948)

CLINICAL PICTURE

Acute ileitis

The majority of these cases simulate acute appendicitis and hence are diagnosed by laparotomy According to Crohn (1949) 25–50 per cent resolve completely but obviously accurate records are impossible to obtain The possible relationship of non specific mesenteric lymphadenitis to acute ileitis is suggested by Jackson (1937) though denied by others (Crohn 1949 Strombeck 1937)

Jejuno-ileitis

The characteristic features are diarrhoea of acute or gradual onset loss of weight, intermittent pyrexia and abdominal pain of variable intensity (Crohn 1949

SECTION II

REGIONAL ILEITIS

(*Synonyms* Terminal ileitis regional enteritis segmental enteritis localized hyper trophic enteritis hypertrophic jejuno ileitis ileocolitis chronic intestinal enteritis ileitis terminalis stenosans chronic cicatrizing enteritis ileitis ulcerosa entero *colitis*)

INTRODUCTION

THE principal features of regional ileitis the most generally accepted term are those of a chronic fibrosing lesion involving the intestinal tract particularly the terminal ileum Such chronic intestinal granulomas were first described in 1813 by Coombe and Saunders but the aetiological factors concerned still elude detection Though the main clinical emphasis has been on chronic lesions care ful observation has demonstrated that acute subacute and chronic ileitis may be regarded as manifestations of the same disorder The relevant literature and clinico pathological data have been admirably presented by Crohn (1949)

PATHOLOGY

Three stages can be recognized—acute subacute and chronic Each type may present alone or in association with either or both the other two stages in other parts of the intestine Both the acute and subacute phase and even an early stenosing lesion may undergo resolution and cure Any portion or length of the alimentary tract or multiple localized areas may be involved

Histologically the acute phase shows oedema hyperaemia mononuclear cell infiltration and dilated lymphatics principally affecting the submucosal coat In the subacute phase oedema and hyperaemia are less marked Collections of round cells are seen and in places actual giant cell formation occurs In addition there is a tendency to form fibrous tissue In both these phases the mucosa may become ulcerated and with ulceration further secondary changes are brought about by the invading bacteria and intestinal contents Such ulceration may on occasions progress rapidly through all the layers of the intestine leading to perforation or should the peritoneal reaction have been sufficiently rapid to cause adherence of the adjacent viscera to fistula formation When secondary infection takes place the histological pattern becomes distorted and the primary picture unrecognizable In the chronic stage fibrosis predominates so that the orderly arrangement of the intestinal wall is deranged and thickened and the lumen narrowed In such cases the wall above the stricture is dilated and hyper trophied All degrees of fibrosis may be encountered from a lesion which is entirely fibrotic to one that is a mixture of fibroblasts plasma cells and giant cells

CLINICAL PICTURE

The mesenteric lymph glands are usually enlarged though this is not invariable Histological examination shows all variations of reaction oedema non specific inflammation necrosis giant cell formation and fibrosis (Crohn 1949 Hadfield 1939 Warren and Sommers 1948 Schepers 1945)

To sum up regional ileitis though clinically a distinct entity has no pathognomonic histological features

AETIOLOGY

In spite of many attempts to isolate a specific bacterial agent (Pumphrey 1938) none has been successful Viruses animal parasites bacterial toxins foreign bodies impairment of blood supply appendiceal inflammation neurotropic disturbances hormone imbalance and vitamin deficiencies have all been suggested On the basis of the similarity of the pathological findings some workers consider that the tubercle bacillus is the cause of the disease (Bockus 1945) and the possibility of sarcoid has also been put forward (Hadfield 1939 Crohn 1939)

Experimentally Reichert and Mathes (1936) produced intestinal oedema and fibrosis by the injecting of the lymphatics of the small bowel mesentery of dogs with finely divided sand and other sclerosing solutions In humans however obstruction of the lymphatics frequently cannot be demonstrated More convincing are the results of Chess and others (1950) who produced in dogs changes indistinguishable from regional ileitis following feeding fine sand These changes were found principally in the terminal ileum though the whole small intestine was involved with the exception of the duodenum In 2 of their 15 dogs granulomas also occurred in the liver If in addition to feeding sand an injection of viable bacteria was made an ulcerating enteritis was superimposed upon the reactive picture already produced They drew attention to the possible harmful ingestion of certain types of tooth paste and certain industrial occupations as possible causes of the condition in man These experiments appear highly significant pointing to a non infective or possibly absorptive defect as one of the causes of regional ileitis A number of workers have drawn attention to a relatively high incidence of such substances as talc enmeshed in the pathological reaction (Lightman and others 1946 Warren and Sommers 1948)

CLINICAL PICTURE

Acute ileitis

The majority of these cases simulate acute appendicitis and hence are diagnosed by laparotomy According to Crohn (1949) 25-50 per cent resolve completely but obviously accurate records are impossible to obtain The possible relationship of non specific mesenteric lymphadenitis to acute ileitis is suggested by Jackson (1937) though denied by others (Crohn 1949 Strombeck 1937)

Jejuno-ileitis

The characteristic features are diarrhoea of acute or gradual onset loss of weight intermittent pyrexia and abdominal pain of variable intensity (Crohn 1949

Sussman and Wachter 1942) The faeces contain large amounts of fat while macrocytic anaemia and low serum proteins may develop In the most severe *examples extreme inanition and dehydration occurs The process may resolve* completely or proceed to a chronic stage with multiple fibrous strictures In the absence of laparotomy the diagnosis on clinical grounds is impossible to differentiate from idiopathic steatorrhoea though persistent abdominal pain without gross distension favours jejuno ileitis The condition may be perhaps best illustrated by two examples

S W female aged 14 years First seen on account of loss of 2 stone in weight in 6 months mild abdominal pains and loose pale stools 4–5 times daily for 3 months On admission to hospital she was pyrexial occasionally as high as 103 F Examination showed mild finger clubbing no abnormality in the heart or chest but the abdomen



Fig 191 —Radiograph of jejuno ileitis in a girl aged 14 years showing the irregular mucosal outline and lack of normal mucosal *pattern* (Raybar meal)

was distended dough like and markedly tender to the right and left of the umbilicus Laboratory findings showed sedimentation rate 42 millimetres per hour 4 49 million red cells 11 6 grams haemoglobin with 12 000 W B C of which 76 per cent were polymorphonuclears Liver function tests proteins and electrolytes were within

normal range Fat absorption tests showed 45–70 per cent absorption in a large number of tests over 3 months Mantoux skin-test was negative on 3 occasions to tuberculin 1 1000 Radiograph of chest was normal but that of the small intestine showed an abnormal pattern similar to that illustrated in Fig. 191

With a high-protein, low fat, low-residue diet, she continued to lose weight despite cessation of diarrhoea though not of steatorrhoea, and to complain of severe attacks of abdominal pain sufficient to cause nausea and vomiting. Laparotomy was therefore carried out and revealed that the small intestine was hyperaemic and somewhat oedematous. The mesenteric glands were generally enlarged, the maximum size being approximately 1 centimetre which on biopsy showed multiple giant-cell formations but no evidence of tuberculosis on culture She improved following laparotomy and the administration of calciferol regaining 2 stone in weight Observations over the past 18 months have shown that her fat absorption has returned practically to normal range though her weight remains stationary 2 stone below her weight prior to illness Her sedimentation rate is still elevated 20 millimetres per hour and she still has occasional attacks of diarrhoea and abdominal pain. Her pancreatic enzymes are normal, glucose tolerance tests have been both flat and normal on different occasions. Liver function tests have remained satisfactory while the white cell counts are now within normal range Radiological examination show no definite improvement the coils appearing thickened and the mucosa abnormal. There is however no evidence of stenosis She remains intolerant of fat and still easily fatigued. She is being treated with bed-rest and diet.

E. M., female aged 64 years Four months prior to admission she developed attacks of diarrhoea 4–10 days in duration 3–8 stools per day watery and offensive with periods of freedom of 1–3 weeks loss of weight and lassitude On admission she had a macrocytic anaemia, 3 87 million red cells, 12 8 grams haemoglobin, M C V 103 3 gross steatorrhoea (fat absorption 28 per cent) and, radiologically an intestinal picture indistinguishable from that of severe idiopathic steatorrhoea. In hospital she had only occasional mild abdominal pain and gained weight. 14 months later having again lost weight onset of severe abdominal pain compelled admission to hospital Laparotomy showed 15–20 localized areas of oedema and fibrosis in the upper 6 feet of the jejunum, causing partial obstruction. A side to-side anastomosis was performed leaving the affected part by passed but not excluded. Four months later she was admittedly severely ill following perforation in the by passed segment. She died the day after operation. Pathological report "The appearances are non specific but are consistent with focal sclerosis of the post-granulomatous stage of Crohn s disease"

Ileocolitis

Involvement of the caecum and ascending colon occurs in small numbers of chronic regional ileitis and occasionally only the colon may be involved and simulate carcinoma In the subacute form such cases may be mistaken for ulcerative colitis (Crohn and others 1947) Such mistakes are readily made since the ileum may be secondarily involved by retrograde extension in 25 per cent of cases of ulcerative colitis (Crandon and others 1944 Warren and Sommers 1948) In ileocolitis on the other hand the colon appears to be secondarily affected and then it is the proximal colon that is involved though with progress of the lesion the process appears to pass distally In effect, therefore there is a subacute form of regional ileitis affecting the ileum and colon similar to jejuno-ileitis

In mild cases the principal complaint is 4–5 loose and often pale stools a day Mucus may be obvious blood in the stools is rare though melaena occasionally occurs Pus cells are few though fatty acid crystals are common In the early stages *constitutional* upsets are minimal but radiological examination reveals changes in the terminal ileum usually dilatation poor mobility and changes in the *mucous pattern The colon shows smooth* outline and reduction of haustration similar to that described as mucous colitis (*Fig* 192) Examination of fat



Fig 192 —*Radiograph of 17 year-old schoolgirl* showing the abnormal colon Owing to the pelvic caecum the terminal ileum is not visualized The only symptoms are 4 6 loose bulky stools daily without pus or blood but containing exce s fat (fat absorption 86 per cent) *Constitutionally she is* doing well academically and athletically

absorption shows mild defects 80–90 per cent A mild leucocytosis may be present With persistence of the di order the colon takes on more permanent changes in the ascending and transverse colon (Fig 193) Sigmoidoscopy reveals a red velvety mucous membrane without ulceration though bleeding easily on touch Con stitutionally the full steatorrhoea syndrome may *eventually develop macrocytic anaemia* low serum proteins splenomegaly and gross impairment of fat absorption



FIG 193—Ileocolitis Radiograph (Raybar meal) showing the abnormal mucosal pattern and dilatation of the terminal ileum and extensive changes in the colon of a 4 year-old woman with gross steatorrhoea refractory macrocytic anaemia low serum proteins and 4 8 stools daily Sigmoidoscopy has shown mild oedema of mucosa but no evidence of ulcerative colitis Microscopical examination of faeces has shown occasional red cells but no pus These finding have been constantly present since she first came under observation in 1946

Chronic regional ileitis

Crohn (1949) has stressed the frequency of diarrhoea and relatively long periods of prodromal symptoms terminated by subacute intestinal obstruction or the formation of a mass or fistula These mild symptoms of intermittent diarrhoea malaise loss of weight occasional pyrexia had lasted 1–5 years in more than half of a series of 183 patients he reported Pain was present in only half of 222 cases When pain does occur it is often related to food so that peptic ulceration may be simulated Recurrent abdominal pain in association with intermittent diarrhoea and loss of weight should however always lead to careful radiological examination of the small intestine When symptoms of obstruction perforation or fistula formation become apparent the diagnosis is self-evident though by that time extensive secondary changes will have made treatment difficult

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Other laboratory findings

Fractional test meals glucose tolerance tests chylomicrographs may be normal or abnormal in any given patient and show no diagnostic feature Electrolyte metabolism as in the steatorrhoea syndrome is easily upset and hypokalaemia is not uncommon In those patients who have suffered a recurrence the serum proteins tend to be low

Treatment

Many consider that the treatment is essentially surgical directed to the excision of all tissues involved This claim is supported by the eventual necessity for surgery in most patients with regional ileitis owing to the complications of stricture fistula or perforation Opposing this view the complete resolution in acute ileitis and the occasional chronic case together with the impracticability of dealing with extensive lesions in the subacute stage supports the claims of conservative medical treatment as the basis of any therapy in this disorder This as Kieffer and others (1950) state should be a constantly controlled regime for the patient whether operated upon or not It is to be preferred in acute ileitis granulomatous jejuno ileitis and ileocolitis in localized disease of short duration without complications or in long standing lesions which have shown no tendency to progress and lastly in those patients who refuse operation

The principles of treatment may be laid down as adequate bodily rest maintenance of nutrition with a high calorie high protein diet the control of diarrhoea (and possibly even the spread of the disorder) by a low fat diet and lastly the correction of secondary effects stenosis fistula formation or perforation

Jejuno ileitis requires long periods of bed rest with a high protein low fat diet Periods of six months or more may be necessary before remission sets in with the restoration of absorptive function Ileocolitis responds well to similar measures In either state treatment may be necessary for anaemia which as in the steatorrhoea syndrome may be difficult to eradicate The adoption of a sanatorium regime even in patients with a palpable mass and confirmatory radiological findings leads to great constitutional improvement and occasionally complete resolution of the lesion

The mere persistence of extensive radiological signs is not in itself an indication for surgery as was pointed out by Cutler (1939) and is illustrated in Fig 194 Surgical intervention is required if repeated subacute intestinal obstruction fistula formation abscess or perforation occurs It is also indicated in those patients in whom in spite of adequate rest and diet constitutional symptoms persist in the presence of radiological evidence of the disorder Such patients are liable to progress to fistula formation or perforation Even though the disease be no longer active the resultant stenosis may be sufficiently severe to cause gross dilatation of the intestine proximal to the lesion Such intestinal dilatation even in the absence of constitutional upset calls for operation for sooner or later a secondary enteritis or macrocytic anaemia will develop Such intestinal dilatation occurs frequently in cases who have already undergone resection Radiologically it may be difficult to differentiate dilatation in the proximal bowel from the gross distension that may take place in the blind loop of the ileum or colon In either event however laparotomy is indicated

DIAGNOSTIC FINDINGS

Radiology

Prior to laparotomy radiology offers the most convenient and accurate method of diagnosis but examination by both barium meal and barium enema may be necessary before the whole intestinal tract is visualized satisfactorily The characteristic features of the condition have been well described by many workers (Kantor 1934 Finkelstein 1950 Crohn 1949) Non flocculating barium (Arden and others 1950) should be used if errors are to be avoided and minor degrees of stenosis satisfactorily defined and repeated radiological examination may be necessary before the lesion can be clearly seen

Haematology

Crohn noted a progressive anaemia in many of his patients In only one who had undergone two previous resections for ileitis was a pernicious anaemia type of blood picture encountered Plum and Warburg (1939) however reported 3 such cases in detail occurring prior to any operative treatment and 6 of the 7 patients mentioned by Butt and Watkins (1936) had a macrocytic anaemia In this clinic of the 16 patients examined prior to resection 7 had definite macrocytosis of which 2 had a moderately severe anaemia Of 9 further patients seen with symptoms following resection 7 had a well developed macrocytic anaemia including 2 patients with red cell counts of 1 5 million The development of such anaemias appears directly related to both the duration and the extent of the lesion whilst any patient who has undergone resection is liable to develop haematological findings essentially similar to those seen in idiopathic steatorrhoea As Crohn states most patients will present with little or no upset in the red cell count and haemoglobin concentration Even at this stage however absolute values or a Price Jones curve may reveal evidence of an incipient macrocytic anaemia On the other hand in the subacute phase macrocytic anaemia is the rule rather than the exception occurring in 3 out of 4 patients with jejuno ileitis and 5 out of 8 patients with ileocolitis The morphological features of the peripheral blood differs in no way from those seen in the steatorrhoea syndrome

White cell counts give no specific aid in diagnosis though with ulceration and abscess formation leucocytosis may occur

Faeces

Melaena may occur in any stage of regional ileitis Microscopically there may be no abnormality detected but in some excess of fatty acid crystals occasional red blood cells and rare pus cells may be seen

In all 4 patients with jejuno ileitis fat absorption was severely impaired though with remission 2 regained normal fat absorptive powers the other 2 died In all 8 cases of ileocolitis fat absorption was defective Of 9 patients with chronic regional ileitis examined prior to operation 3 had a marked fat absorption defect and 2 slight impairment whilst the remainder were within normal range and remained so in spite of the resection of 3–5 feet of small intestine In 11 others not examined prior to operation moderate to marked impairment of fat absorption was demonstrated in all

FURTHER REFLECTIONS UPON AETIOLOGY

The occurrence of oedematous intestines and swollen mesenteric glands together with the histological picture has caused infection to be considered the most likely aetiological factor The failure to find such an infective agent does not necessarily rule out the possibility of it being the initiating factor in a series of tissue reactions

Chess and his colleagues (1950) show clearly that non infective agents may produce changes indistinguishable from regional ileitis and that such changes are produced as a direct consequence of the absorption of abnormal products It is more than possible that a variety of compounds may possess this property of stimulating reactions of this nature For example Hirsch (1941) has pointed out that fatty acids produce effects upon the tissues depending upon the degree of acidity produced the soap formed and lastly the structure of the fatty acid Thus fatty acids such as stearic when separated from liquid fat in the tissues cause the tissue stimulus of a solid substance and the formation of foreign body giant cells Human fat containing a low concentration of free oleic acid and stearic acid neutralized with calcium hydroxide stimulates a moderate fibroblastic reaction If n utralized with barium hydroxide the mixture causes a marked reaction with epithelioid and giant cells Hass (1938) concluded that formation of multi nucleated giant cells was a consequence of hydrolysis of fat with liberation of an acid having a higher melting point above the tissue environment and that cyclopentyl fatty acid esters produced abscesses or marked scar tissue Theoreti cally therefore it is possible that the histological picture of regional ileitis is the result of fat breakdown either as the result of alteration of local tissue enzymes or as a result of local reaction to the absorbed abnormal products of a faulty digestion In either event the histological pattern will be the same and it is not therefore surprising that Reichert and Mathes were able to produce analogous histological changes by altering local tissue reactions through the injection of sclerosing agents into the lymphatics

In this clinic therefore interest has been taken in the role that mal absorption of fat might play While actual steatorrhoea occurs in many patients prior to operation it does not do so in all It is therefore difficult to exclude the occurrence of stenosis as the primary cause of steatorrhoea rather than *vice versa* though following operation a few patients present the fully developed steatorrhoea syndrome without evidence of any such stenosis It is true that the e patients had suffered the loss of intestine which could possibly account for this but in two of the patients the resection of 3-5 feet of intestine did not result in steatorrhoea so that resection cannot always be the explanation

If there should be any substance to this theory then some pati nts with idiopathic steatorrho a should develop regional ileitis We have encountered no proven case except possibly case E M quoted above One other patient has been under observa tion 8 years with symptoms and radiological findings compatible with idiopathic steatorrhoea and is now developing signs symptoms and radiological appearances suggestive of ileitis Avery Jones (1950) has encountered one patient in whom the change from coeliac disease to jejuno ileitis appears probable

In this clinic one patient with ileocolitis has a sister with idiopathic steatorrhoea Another with regional ileitis is the son of a patient with idiopathic steatorrhoea

The surgical details of operation have been adequately described by many workers (Marshall 1943 Brown and Donald 1942 Garlock and Crohn 1945 Lewisohn 1938) The consensus of opinion is that by passing the lesion with removal of the affected loop in one or two stages is *the operation of choice* If the loop be not excluded marked steatorrhoea and anaemia will ensue in most



Fig 194 —Male aged 54 years Radiograph in 1943 showing extensive involvement of distal ileum Arrow points to area not completely filled but which is also involved by the stenosing process This patient has been working regularly since 1945 He has occasional abdominal colic with diarrhoea His blood count remains at 3 5-4 0 million red cells with 90-100 per cent haemoglobin despite treatment He takes a high protein low fat low residue diet His most recent radiograph (1951) is similar to that taken in 1943

cases Surgical excision is usually followed by increased laxity of stools Since varying degrees of steatorrhoea are commonly present a low fat diet will control this symptom Unfortunately neither medical nor surgical treatment can guarantee cure The most that can be claimed *is remission though with the passage of years* the likelihood of recurrence becomes more remote (Hadfield 1939 Kieffer and others 1950)

REFERENCES

Fradkin W E (1948) *Amer J digest Dis* 15 119
Garlock J H and Crohn B B (1945) *J Amer med Ass* 127 205
Hadfield G (1939) *Lancet* 2 773
Hass G M (1938) *Arch Path* 26 1183
Hirsch E F (1941) *Ibid* 31 516
Jackson A S (1937) *Surg Gynec Obstet* 65 1
Kantor J L (1934) *J Amer med Ass* 103 2016
Kieffer E D Marshall S F and Brolsma M P (1950) *Gastroenterology* 14 118
Killian S T and Ingelfelder T J (1944) *Arch intern Med* 73 466
Lewisohn R (1938) *Surg Gynec Obstet* 66 215
Lightman A L McDonald J R Dixon C F and Mann F C (1946) *Ibid* 83 531
Marshall S F (1943) *Surg Clin N Amer* 23 873
Mock H F (1931) *Surg Gynec Obstet* 52 672
Plum P and Warburg F (1939) *Acta med scand* 102 449
Pumphrey R E (1938) *Proc Mayo Clin* 13 539
Reichert M L and Mathes M E (1936) *Ann Surg* 104 601
Schepers G W H (1945) *Amer J digest Dis* 12 91
Strombeck J P (1937) *Acta chir scand* 80 *suppl* 501
Sussman M L and Wachter E (1942) *Amer J Roentgenol* 39 48
Warren S and Sommers S C (1948) *Amer J clin Path* 24 475

Moreover in two generations of this family there are 6 further cases of idiopathic steatorrhoea Crohn has reported 11 instances of a familial association with regional ileitis

Though such evidence is encouraging it is apparent that this hypothesis is not readily amenable to proof in the absence of previous laparotomy for the finding of regional ileitis irrespective of the history automatically excludes the diagnosis of idiopathic steatorrhoea It is however worth recalling the histories of the cases recorded by Crohn In the majority history of intermittent diarrhoea in half of which there was no pain occurred for 3–5 years prior to diagnosis whilst in one case the history had extended over 50 years Some might well have simulated idiopathic steatorrhoea A further link is suggested by study of Whipple s disease idiopathic steatorrhoea and jejuno ileitis A relationship between these conditions has been postulated by Avery Jones and Paulley (1949) Examination of a series of patients with steatorrhoea and mesenteric lymphadenopathy in Birmingham has revealed much difficulty in differentiating Whipple s disease in some patients from idiopathic steatorrhoea and in others from jejuno ileitis In view of the observations already cited it is perhaps not surprising that difficulties in interpretation should arise The histological changes can be regarded as a specific reaction to the breakdown of certain fat complexes though as non specific in respect to the factor initiating such reactions Such local tissue reactions may be initiated as the result of defects of digestive enzymes within the intestinal lumen due to constitutional nutritional or infective factors or as the result of changes in the intestinal wall which in their turn may be nutritional (Killian and Ingelfelder 1944) infective (Felson 1936 Fradkin 1948) or traumatic (Mock 1931 Crohn 1949)

To sum up the view is put forward that regional ileitis is the result of tissue reactions to the breakdown products of absorbed lipoid complexes or possibly other metabolites or ingested substances leading to further defects in absorptive powers These may be temporary or persist and aggravate the lesions already present Infection nutrition enzyme deficiencies or trauma may be involved in initiating this sequence of events

REFERENCES

Arden G M French J M and Mucklow E H (1950) *Brit J Radiol* 23 697
Avery Jones F and Paulley J W (1949) *Lancet* 1 214
— (1950) Personal communication
Bockus H L (1945) *J Amer med Ass* 127 449
Brown P W and Donald C J (1942) *Amer J digest Dis* 9 87
Butt H R and Watkins C H (1936) *Ann intern Med* 10 222
Chess S Chess D Olander G Benner W and Cole W H (1950) *Surgery* 27 221
Combe C and Saunders W (1813) *Med Trans Roy Coll Phys Lond* 4 16
Crandon J H Kinney T D and Walker I J (1944) *New Engl J Med* 230 419
Crohn B B (1939) *Surg Gynec Obstet* 68 314
— (1949) *Regional Ileitis* London Staples Press Ltd
— Garlock J H and Garnis H (1947) *J Amer med Ass* 134 334
— (1949) *N Y St J Med* 49 1808
Cutler E C (1939) *Ibid* 39 328
Felson J (1936) *Ann intern Med* 10 645
Finkelstein A (1950) *Postgraduate Gastroenterology* Philadelphia Bockers Saunders

technique has been used by Schatzski (1943) (the small intestine enema) Double contrast enteroclysis (barium and air) has been used by Gershon Cohen and Shay (1939) The accelerating effect of an ice cold drink after initial screening has been used by Weintraub and Williams (1949) The large amounts used by the Schatzski method tend to obscure much detail by superposition of coils

Flocculation

Recognition of the unsatisfactory nature of the common preparations for contrast work has led to the exploration of the use of many different types of suspending agents Apart from the use of the common gums such as tragacanth and acacia there have been trials of colloidal aluminium hydroxide (Woldman

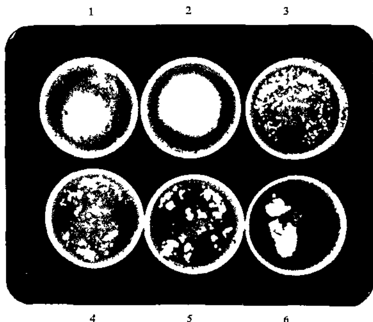


FIG 195—Skiagram of 6 petri dishes each containing 1 gram of barium sulphate suspended in 15 millilitres of water Increasing quantities of mucus containing secretion added to each from 2 6 Mixtures were rocked and poured on to plates Note increasing size of floccules with increasing amount of mucous secretion (*By courtesy of British Journal of Radiology*)

1938) gelatine (Abel 1944) and prepared gastric mucin (Alexander and Alexander 1950) colloids of an undisclosed nature have been used (Jones Kaplan and Windholz 1951 Zimmer 1951) In an attempt to improve the penetration of mucus micropulverization has been carried out (Adolph and Taplin 1950) Contrast media other than barium have been tried such as thorium dioxide and iodinated compounds This work has been mainly for the purpose of improving

CHAPTER 21

RADIOLOGICAL ASPECTS OF THE SMALL INTESTINE IN STEATORRHOEA

J M FRENCH

THE radiological examination of the small intestine is carried out with three aims the examination of structural integrity motility and mucosal pattern

Technique

Examination is carried out with the barium meal A simple follow through series of films is commonly employed and after routine screening of the oesophagus stomach and duodenum films are taken at short intervals in the prone position films at 3 4 6 and 8 hours are taken for views of the ileum occasionally further films are necessary At some time during this period screening of the terminal ileum is carried out preferably as the head or the tail of the meal is entering the caecum Frequently the terminal ileum may be satisfactorily seen by retrograde filling from a barium enema

EXAMINATION FOR STRUCTURAL INTEGRITY

Importance of fluidity of contrast medium

In order to examine the small intestine satisfactorily for gross pathological changes in anatomy such as strictures fistulae and for lesions of the mucous membrane and changes in mucosal pattern it is necessary to maintain the contrast medium in a state of fluidity sufficient to enable such changes to be demonstrated Although a dilute suspension of barium sulphate is commonly used and further dilution may occur in the stomach two influences combine to render it more and more concentrated once it has passed through the pylorus namely (1) water absorption and (2) flocculation

Water absorption

One of the main functions of the small intestine is the absorption of water As this is the vehicle of the barium sulphate the latter becomes progressively more concentrated as the meal passes down the intestine Early in the meal when it is still fluid fine mucosal detail is seen in the jejunal areas but by the time the meal has reached the ileum and often before it has become converted into a pasty mass by the absorption of its water content and may appear broken up into a series of boluses without any mucosal detail being visible The slower the transit the higher in the bowel is this concentrated appearance seen conversely the more rapid the transit the more mucosal detail is seen Any procedure therefore which leads to rapid passage of the barium through the intestine will improve visualization of the ileum With the object of maintaining fluidity the duodenal intubation

visualization of the stomach and colon though improved detail in the small intestine has been sometimes observed It has been carried out however without an understanding of the fundamental part played by mucus in the problems of flocculation and sedimentation

It has recently been shown that simple suspensions of barium sulphate in water (or saline) undergo flocculation in the presence of freshly secreted mucus whether of salivary gastric small or large intestinal origin (Frazer French and Thompson 1949) Gastric mucus has been shown to cause flocculation over a wide pH range (1 5–8 0) Such flocculation occurs on a quantitative basis (Fig 195) and the floccules formed separate out from the water by adhering to each other until they may become one concentrated mass If flocculation occurs in the intestine due to an excess of mucus the barium becomes concentrated and there is a loss of fluidity of the contrast medium which prevents it flowing into the mucosal folds entirely false outlines may be seen (Fig 196 (*a*) and (*b*)) Some stable complex colloid suspensions of proprietary origin appear to be protected to a limited extent against flocculation by mucus The use of such preparations may give fine mucosal detail in the presence of an excess of mucus (Ardran French and Mucklow 1950 Astley and French 1951) Stabilization of suspensions with acacia mucin pectin or tragacanth is not sufficient to prevent flocculation (French 1951)

Forms of structural change associated with defective fat absorption

Alterations in the route taken by barium suspensions may readily be seen in the following conditions in which defective absorption of fat is a common feature gastrectomy gastro jejunostomy gastro jejuno colic fistula—in many cases of the latter however a barium meal may persistently fail to show a fistulous opening which is easily demonstrable by barium enema For this reason in cases of steatorrhoea developing some months or years after gastro enterostomy or other operation for peptic ulceration it is not possible to exclude a fistula by barium meal examination alone

Fistulous connections may less readily be seen in entero enterostomies entero colic fistulae and in conditions entailing the formation of a blind loop Multiple diverticula of the small intestine are sometimes seen in association with defective fat absorption but the aetiological relationship is not clear The many different radiological appearances of the small intestine associated with regional enteritis and ileocolitis have been reviewed by Crohn (1949) and Bockus (1950) The studies relate to simple flocculable suspensions of barium sulphate but the recognition of the different pictures which may be seen with flocculating and non flocculating suspensions (Ardran and others 1950) may lead to considerable modification of the views at present held as to the significance of these changes

EXAMINATION OF MOTILITY

Alterations in motility may conveniently be measured in terms of (1) transit time and (2) segmental and peristaltic movements

The methods of examination of these factors include the barium meal with still photographs screening cinematograph recordings and intubation methods with kymographs



FIG 196 — 10 gram of barium sulphate placed in a segment of ileum removed *post mortem* Note even distribution of barium (*a*) Mucus secretion was then added and the barium allowed to flocculate Note the segmentation of the barium with clump formation and clearance of the barium from intervening portions Constricted shadows are seen which are clearly not caused by hypertonia of the intestinal wall (*By courtesy of British Journal of Radiology*)

(*a*)



(*b*)

Observations in the sprue syndrome

It is still contended by a number of authors that defective absorption in these conditions is due to small intestinal hurry A number of radiological studies with simple barium meals (*reviewed by Golden 1945*) have shown that transit through the small intestine is delayed in advanced cases (which have the most severe defect) and within normal limits in the less severe Whether these studies may be regarded as significantly related to what happens to food in the sprue syndrome is not known as no studies with added food have been reported

Segmental and peristaltic movements

Examination of these can be made by screening Permanent records are not available and critical appraisal is therefore difficult The need for more detailed movement studies has directed attention to the possibilities of cinematography by direct exposure of continuous x ray film with reproduction on microfilm for study (Barclay 1939 Alvarez 1948 McLaren Ardran and Sutcliffe 1950) Indirect cinematography (filming of the fluorescent screened image) has also been used (Kawaishi 1938 de Castro 1947) The main advantages of these methods is that definition is far superior to that seen with simple screening (which is limited to rod vision) and permanent records are obtained which can be repeatedly seen and analysed by examination of the looped microfilm The great disadvantage is the high amount of radiation required for records of relatively short periods (minutes or less) of a barium meal which may last for hours Such brief records may give rise to biased views of the general picture

MUCOSAL PATTERN

In normal adult subjects

Using simple suspensions of barium sulphate in water or normal saline (flocculable)

In normal subjects the small intestine pattern shows a fairly typical sequence in the duodenum and jejunum the pattern is of a feathery or herring bone type in a more or less continuous column of regular width of 2–3 centimetres (Fig 197) Sometimes the duodenum may show a pavement type of pattern which is capable of rapid changes to feathery and back again to pavement (McLaren and others 1950) The feathery appearance is followed by a snowflake appearance (Fig 198) which has been regarded as due to barium residues in hypothetical vasa digestiva (Forssell 1923) From the studies of mucus flocculation it appears probable that the flakes are simply residues of barium sulphate flocculated with small amounts of mucus This appearance is not seen in the ileum

In the ileum which is narrower than the jejunum the appearance is usually a series of small irregular boluses (Fig 198) or the lumen may be filled for considerable lengths with densely packed barium Detailed mucosal pattern is only seen occasionally the folds may then be seen arranged transversely suggesting coins stacked closely one upon the other (Fig 199) though a feathery appearance of the folds is sometimes seen (Fig 200)

Using complex non flocculating barium suspensions

The small intestine picture is practically the same as has been described for simple suspensions (Fig 201 (*a*) and (*b*)) with the following differences there is greater continuity of the folds and the shadows are softer The snowflake

Transit time

In the investigation of excessive output of unabsorbed food and water in the faeces a study of the rate of passage of the intestinal contents is important particularly in relation to the understanding of diarrhoea In order to study such a relationship it is essential to examine the small and large intestinal transit times separately and the only means of doing this is radiological

It is usual to assess the small intestine transit time by observing the time after swallowing in which the head of a simple barium meal reaches the caecum the time in which the tail of the meal reaches the caecum is also significant There are wide variations in these times in normal adults and values commonly given are 2 and 6–8 hours respectively If the head reaches the caecum in less than an hour the intestine may be regarded as hypermotile but if the meal has not reached the caecum in 5 hours with the stimulus of food hypomotility is present (Golden 1945) The border line between normal and abnormal is not well defined however and variations in children are even wider than in adults (Henderson 1942)

Although many studies on transit times have been carried out there are indications that these bear a somewhat superficial relationship to the main problem which is the rate of passage of food through the small intestine As the rate of passage through the small intestine is customarily assessed from the time of ingestion of a meal any influence which alters gastric emptying such as the delay caused by fat will have a marked effect upon the times recorded It has been shown that the addition of foods especially fatty has a marked influence upon rate of passage actually in the small intestine and the lack of relationship between the transit times of simple barium meals and those with added foodstuffs has been pointed out (Menville and Ane 1932 Ravdin and others 1936 Reynolds and others 1940) Ravdin and others have suggested that a standard suspension of barium sulphate in distilled water should be employed for radiological examination but that an ideal meal containing fat protein and carbohydrate should be added for the examination of transit time

Other factors liable to cause an alteration in the rate of passage must also be taken into account the pharmacological action of the contrast medium and the quantity (Golden 1945) and the fact that a contrast medium may travel at a rate different from food even when mixed with it (Wasteneys Crocker and Hamilton 1941) the influence of additives particularly in the flavoured proprietary products the consistency (Grindlay and Mann 1941) the influence of water absorption and water retention (Ravdin and others 1936 French 1951) the difference in rate of passage of flocculated and non flocculated meals (Ardran and others 1950) the period of starvation prior to examination the previous dietary history this is probably of most importance in the examination of infants (Bouslog and others 1935 Teall 1950 Astley and French 1951) but may also influence adults (Frazer and others 1949) The giving of foodstuffs subsequent to the barium meal also has a marked influence as is shown by the fact that radiologists give food to assist in the emptying of the ileum after several hours have elapsed Others give a meal immediately after the initial screening (Weber and Kirklin 1938) Giving food with the contrast medium is a procedure very relevant to the assessment of the rate of passage of food but it appears that there is no standardization of method

Observations in the sprue syndrome

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FIG 197 —Normal feathery mucosal pattern of the jejunum A number of constrictions due to segmental contraction are also seen (non flocculating suspension)



FIG 198 —Normal jejunal pattern showing snowflake appearance as the meal progresses The barium has become concentrated in the ileum and is seen as a series of boluses (barium water)



Fig 199—Normal ileal pattern Continuous mucosal pattern in the ileum of the stacked coin variety the bowel appearing relaxed Transverse folds are seen packed together (non flocculating suspension)



Fig 200—Normal ileal pattern Feathery appearance the ileum appears for the most part narrow and a number of segmentally contracted areas may be seen (non flocculating)



FIG 201 —Normal jejunal pattern (*a*) Using simple suspension of barium sulphate in water (*b*) using complex non flocculating suspension Fine feathery detail is shown in both which are practically indistinguishable (same subject)

(*a*)



(*b*)

FIG 202.—Normal jejunum in a child of 7 years (*a*) Bolus type with barium water suspension (*b*) feathery type with non-flocculating suspension. (*By courtesy of British Journal of Radiology*)



(*a*)



(*b*)



(*a*)

FIG 203 —Small intestine pattern of a case of idiopathic steatorrhoea with barium water suspension (*a*) 1 hour (*b*) 2 hours Gross floccule formation



(*b*)



FIG 204 —Small intestine pattern of case of idiopathic steatorrhoea (*same as Fig 203*) *with barium* water (*a*) 1 hour (*b*) 2 hours On this occasion barium has run rapidly through the intestine to give ladder pattern Flocculation occurs later (2 hours) *see* (*b*)

(*a*)



(*b*)

appearance is not seen transit is usually more rapid and the ileal pattern is more frequently visualized

In normal infants and children

Using simple (flocculable) suspensions

The appearance in infants is quite different from that seen in adults practically no mucosal detail being seen in the upper intestine comparable with the feathery pattern of the adult jejunum The meal is broken up into a series of irregular boluses an appearance known as segmentation This segmented or flocculated appearance may be seen in practically all infants (Bouslog and others 1935 Henderson 1942) and in many children up to the age of 11 years (Zwerling and Nelson 1943) (Fig 202 (*a*)) It is thought to be due to the presence of mucus (Astley and French 1951)

Using complex (non flocculable) suspensions

Considerable fine mucosal detail of the feathery type is seen in the jejunum (Fig 202 (*b*)) though it is not as clearly seen as in the adult In the ileum the meal is usually of the bolus type as concentration occurs

Mucosal pattern in subjects with defective fat absorption

Significant alterations from the pattern described for normal subjects have been observed in a number of states in which there is a defective fat absorption The most frequently observed changes are those occurring in the sprue syndrome



FIG 205 -Jejunum post mortem appearance Valvulae conniventes shown no feathery pattern is seen in this atonic condition and the folds arranged transversely are similar in appearance to that seen in life in cases of the sprue syndrome with non flocculating suspensions and sometimes with flocculating suspensions (Fig 204 (*a*)) (*By courtesy of British Journal of Radiology*)

Fig 206—Influence of position of subject on radiographic pattern (a) Prone position allows the pattern to be well visualized and shows the characteristic ladder pattern in a case of idiopathic steatorrhoea (b) the upright position shows no sign of the ladder pattern The barium is mainly in the pelvis showing dense collections with fluid levels present Skiagrams taken within 5 minutes of each other with non flocculating suspension



(a)



(b)

These comprise alterations in the mucosal relief especially of the jejunum consisting of smoothing of the contours of the lumen obliteration of the markings of the valvulae conniventes and clumping of the barium in elongated masses (Mackie 1933 Snell and Camp 1934) (Fig 203 (*a*) and (*b*)) Some similar findings have been recorded in cases of obstructive jaundice pancreatic fibrosis mesenteric lymphatic obstruction kwashiorkor and gastro colic fistula It may also be seen in some other conditions The literature is reviewed by Golden (1945) and Frazer and others (1949) (studies in the literature refer only to simple suspensions) In some cases of tropical and non tropical sprue it has been observed that there is increased width of the intestine and widening of the valvulae conniventes and the spaces between them (Mackie and Pound 1935) This appearance is regularly seen with the use of the non flocculating suspensions but it may also be seen with flocculating suspensions if they are carried rapidly down the intestine before flocculation and segmentation occur (Fig 204 (*a*) and (*b*)) This wide barred ladder appearance is very like that seen in post mortem preparations of jejunum (Fig 205) and is probably due to an alteration in tone of the muscularis mucosae Although the ladder appearance is regularly seen with the non floccul ting sus pensions in the prone position it is not seen in the upright due to gravitational changes in the distribution of the barium and the direction of the radiation (Fig 206 (*a*) and (*b*))

MECHANISM OF PRODUCTION OF THE FLOCCULATED PATTERNS

Mucus

Flocculated patterns similar to those in the sprue syndrome have been induced in normal human subjects by the intraduodenal injection of substances with a barium suspension (Frazer and others 1949) The substances with which such patterns were induced were hypertonic solutions and long and short chain fatty acids (products of digestion) These substances did not cause gross flocculation of barium sulphate suspensions *in vitro* but *in vivo* were thought to do so by a stimulation of mucous secretion

The fact that mucus can cause gross flocculation of simple suspensions has been amply demonstrated and the observation of two different patterns in cases of the sprue syndrome with the use of flocculable and non flocculable suspensions (Ardran and others 1950) suggests strongly that the clumped pattern in this condition is due to mucous flocculation and that there is an excess of mucus in the small intestine in such cases One of the features of the faeces in the sprue syndrome is an excess of fat in the form of fatty acid The presence of such an excess in the small intestine might be partly responsible for the abnormal mucus content In steatorrhoea of pancreatic origin flocculated patterns are less frequently seen the pattern usually being of the feathery type (Crismer 1948 French 1951) In this disease pancreatic lipase in the small intestine is either diminished or even absent so that little free fatty acid is formed Lowe and others (1950) noted a normal feathery pattern in cystic fibrosis of the pancreas even when fat was fed with the barium meal but if pancreatin containing lipase was also fed the pattern became flocculated The presence of the added lipase would lead to the development of fatty acid from the neutral fat which would stimulate mucus secretion

MECHANISM OF PRODUCTION OF THE FLOCCULATED PATTERNS

Vitamin deficiency

The flocculation pattern was originally termed the deficiency pattern because deficiency states were frequently associated with many of the conditions in which it was described More recently it has been realized that it is not specifically associated with deficiency states that it is seen in subjects in whom there is no evidence of vitamin deficiency and that deficiencies may be induced without the development of the flocculation pattern (Elsom and others 1940) Its presence in normal infants children and occasionally adults and its induction in normal human subjects by intraduodenal injection of specific substances make it unlikely that the absence of vitamins plays any part in the production of these abnormal patterns

Disordered motor function

Golden (1945) has interpreted the pattern as one of disorderly action of the muscularis mucosae and the tunica muscularis He regards the smoothing of the margins of the barium outline as due to changes in tone of the muscularis mucosae narrowing as due to hypertonia and the dilated segmented (clumped) appearance as due to alternating areas of spasm and hypotonia of the muscle coats His view ha developed from observations with flocculating suspensions If flocculation is avoided by the use of the complex suspensions the radiographic appearance in the sprue syndrome is still abnormal a wide dilated appearance being seen There is no evidence to suggest a spastic or hypertonic state of the intestine though there appears to be a loss of tone giving rise to the wide dilated pattern A wide dilated pattern is not commonly seen in pancreatic disease or in regional enteritis As there is often a close similarity between these conditions clinically a small intestine examination is of value in differential diagnosis It is of even greater assistance in the separation of the sprue syndromes from cases of pernicious anaemia in which the pattern is of the feathery typ

Future trends

It seems probable from the recognition of the cause of the flocculated pattern in the small intestine and the increasing adoption of improved suspensions of barium sulphate of the non flocculating type that the radiographic examination of the small bowel will become increasingly useful Cases of the sprue syndrome often masquerade under such diagnoses as mucous colitis nervous diarrhoea carbohydrate dyspepsia lienteric diarrhoea neurasthenia refractory pernicious anaemia *idiopathic tetany and other diagnoses the more frequent use of the* small intestine examination in obscure gastro intestinal disorder may assist in detecting such cases for what they really are as more significance can now be attached to the flocculation pattern The use of the non flocculating suspensions should render the small intestine more easy to examine and it should be possible to develop suspensions which neither flocculate nor become concentrated but pass to the caecum more or less unchanged This will enable the ileum to be examined properly throughout its length a procedure which is at the moment largely a matter of chance

REFERENCES

Abel M S (1944) *Radiology* 43 175
Adolph W and Taplin G V (1950) *Ibid* 54 878
Alexander G H and Alexander R E (1950) *Ibid* 54 875
Alvarez W C (1948) *An Introduction to Gastro enterology* 4th ed London Heinemann
Ardran G M French J M and Mucklow E H (1950) *Brit J Radiol* 23 697
Astley R and French J M (1951) *Ibid* 24 321
Barclay A E (1939) *Radiology* 33 170
Bockus H le Roy (1950) *Postgraduate Gastro enterology* Philadelphia Saunders
Bouslog J S Cunningham T D Hanner J P Walton J B and Waltz H D (1935) *J Pediat* 6 234
Crohn B B (1949) *Regional Ileitis* London Staples Press
Crismer R (1948) *Acta gastro ent belg* 11 511
de Castro M J (1947) *Amer J Roentgenol* 57 103
Elsom K O Lewy F H and Heublein G W (1940) *Amer J Med Sci* 200 757
Forssell G (1923) *Amer J Roentgenol* 10 87
Frazer A C French J M and Thompson M D (1949) *Brit J Radiol* 22 123
French J M (1951) Radiological Studies of the Small Intestine *M D Thesis* University of Birmingham
Gershon Cohen J and Shay H (1939) *Amer J Roentgenol* 42 456
Golden R (1945) *Radiologic Examination of the Small Intestine* Philadelphia Lippincott
Grindlay J H and Mann F C (1941) *Amer J digest Dis* 8 324
Henderson S G (1942) *Amer J Roentgenol* 48 302
Jones H H Kaplan H S and Windholz F (1951) *Radiology* 56 561
Kawaishi K (1938) *Amer J Roentgenol* 40 913
Lowe C U May C D Stauffer H M and Neuhauser E D (1950) *Amer J dis Child* 79 91
Mackie T T (1933) *Med Clin N Amer* 17 175
— and Pound R E (1935) *J Amer med Ass* 104 613
McLaren J W Ardran G M and Sutcliffe J (1950) *J Fac Radiol* 2 148
Menville L J Ane J N (1932) *Radiology* 18 783
Ravdin I S Pendergrass E P Johnston C G and Hodes P J (1936) *Amer J Roentgenol* 35 306
Reynolds L Macy I G Hunscher H and Olson M B (1940) *Ibid* 43 517
Schatzki R (1943) *Ibid* 50 743
Snell A M and Camp J D (1934) *Arch intern Med* 53 615
Teall C G (1950) *Textbook of X ray Diagnosis by British Authors* Vol III p 435 2nd ed London Lewis
Wasteneys H Crocker B F and Hamilton P (1941) *Amer J Physiol* 135 6
Weber H M and Kirklin B R (1938) *Med Clin N Amer* 22 1059
Weintraub S and Williams R G (1949) *Amer J Roentgenol* 61 45
Woldman E E (1938) *Ibid* 40 705
Zimmer E A (1951) *Brit J Radiol* 24 245
Zwerling H and Nelson W E (1943) *Radiology* 60 277

CHAPTER 22

GASTRO INTESTINAL MOTILITY IN MAN

E N ROWLANDS

MANY gastro intestinal symptoms are accompanied by disturbances of motility in some part of the alimentary tract The nature of these disorders is often obscure and treatment empirical because so little is known about the complex motor functions of the gut in man but recent studies have thrown some light on the mechanisms involved in the regulation of motility Experiments on animals are of limited value but investigations on human subjects have been stimulated by the surgery of the autonomic nervous system and the discovery of an ever increasing number of drugs which act upon it and by a better appreciation of the importance of emotional disturbances Unfortunately these new opportunities cannot be adequately exploited until satisfactory techniques are developed to replace the crude methods employed at present

TECHNIQUES FOR STUDYING MOTILITY

Fluoroscopy and cineradiography —Rapid serial radiography is the most physiological method available but radiation hazards impose serious limitations on its use Moreover these methods do not record the muscular activity of the gut but the passage of barium and there is no reason to believe that the bowel reacts to barium in the same way as it does to foodstuffs

Balloon techniques—One or more balloons are inserted into the gut and distended with air or water and the changes of pressure within them are transmitted to manometers and photographed or recorded kymographically The physiological and mechanical limitations of this technique must be fully appreciated in order to interpret the findings in a critical manner The balloon inevitably obstructs the gut to some extent but this can be minimized by using a method which permits the muscular contractions to displace the contained air or water into the recording system thus imitating the passage of intestinal contents from one segment to the next The balloon should be distended only just sufficiently to ensure a satisfactory tracing so that its stimulating effect on the intestinal wall is minimal A good method will register accurately the changes in pressure within the closed cavity formed by the balloon but the mechanical errors inherent in all balloon techniques are such that they cannot be used to measure the actual pressures within the lumen of the gut This fundamental distinction is frequently overlooked and some investigators have drawn unwarranted conclusions by interpreting their results in terms of intraluminal pressures and this has led others to conclude that the method is of no value at all In fact it has yielded important information because the complex muscular activities of the intestinal musculature are mainly responsible

for the pressure changes within the balloon and are therefore recorded in the detailed wave patterns of the tracings and since these are reproducible the method is particularly useful for assessing the effects of drugs on motility

Recording of intraluminal pressures—Brody and Quigley (1947) have devised an accurate method for recording intragastric and intraduodenal pressures in human subjects Open ended tubes of very narrow bore are passed into the gut and the gastro intestinal pressures exerted against their open tips are transmitted to optical manometers by the air columns in the tubes Unfortunately the technical difficulties are formidable but the development of a simple method of measuring the changes in pressure of different parts of the gut simultaneously would be invaluable

Recording of action potentials—It is possible to record motility and action potentials simultaneously in human subjects by intubating with electrodes fixed on to the outer surfaces of balloons More elaborate techniques have been investigated extensively in animals but the significance of the electrical changes is obscure as there is no obvious correlation between them and the muscular contractions

MOTILITY AND THE TRANSPORT OF INTESTINAL CONTENTS

The relationship between motility in the sense of muscular activity and the passage of material through the gut is not at all clear The problem has been rendered even more difficult by a lack of standardization in the use of terms to describe the muscular contractions and by a failure to distingush between motility and the movements of intestinal contents Brief definitions of the various muscular activities are therefore necessary before considering their influence on transport

Motility

Tone—The tonus of smooth muscle has been defined as the resistance which its substance offers to extension and this state of sustained tension is constantly present to some degree in the normal gut and any contractions that occur are superimposed upon it It has been shown by the open tube technique that the gut exhibits basal pressure when no contractions are in the vicinity of the recording tip Tone is represented in kymographic records by the distance between the base line and the level of the writing pen in between contractions (Fig 207) but this is not an absolute measure of tone because it is also influenced by extrinsic factors such as the intra abdominal pressure Fluctuations of tone are common and the slow undulations so formed are sometimes called tonus waves

Segmenting waves—These appear in graphic records as waves of low amplitude and rapid frequency and in radiological studies as a series of ring like constrictions which squeeze small masses of barium to either side and then return them to their original positions in a to-and fro movement which has been described as non progressive segmentation (McLaren and others 1950) This rhythmic segmentation must knead and mix the intestinal contents and facilitate absorption by forcibly smearing the chyme all over the mucosa

Peristaltic waves—These appear in graphic records as tall sustained waves covering a time interval up to two minutes and can be seen travelling down the gut

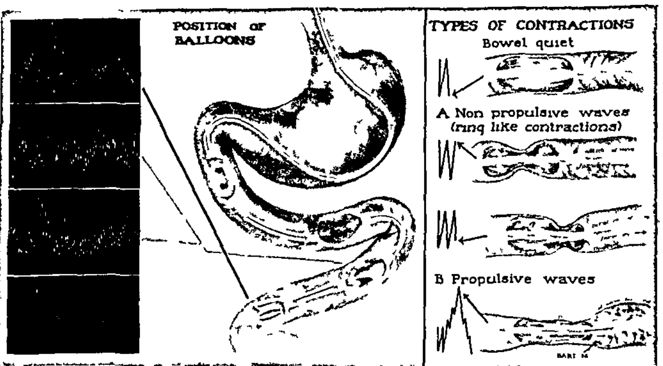


FIG 07—Simultaneous graphic recording and fluoroscopic observation of barium The tracings from the 4 balloons are synchronized and cover a 5 minute period A tall peristaltic wave can be seen appearing first in the lowest tracing (from the most proximal balloon) and finally in the top tracing (from the most distal balloon) (*By courtesy of Journal of Clinical Investigation and Journal of the American Medical Association*)

from one segment to the next when a multiple balloon technique is employed (*Fig* 207) They probably represent propulsive contractions and a number of rapid mixing waves are usually superimposed upon them Peristaltic rushes of barium are occasionally observed in the small gut and correspond to the mass peristalsis movements which occur in the colon

Tonus waves are prominent in the stomach and sequences of peristaltic waves appear intermittently in the region of the antrum *Graphic records from the small* gut and colon show all the above forms of muscular activity but contractions are rarely absent in the upper gut whereas the colon shows only intermittent bursts *of activity at irregular intervals*

Transport of intestinal contents

The tone of the musculature exerts a profound effect on the rate of passage of material through the gut and largely determines the efficacy of the contractions Peristaltic waves diminish progressively in amplitude as the tone rises to a critical level because diastolic relaxation between contractions diminishes until the lumen is finally obliterated by spasm the waves also disappear as tone falls to a low level *Where tone is high as in the upper small intestine the peristaltic waves* are large and numerous and transport is rapid whereas the contents move more slowly in the ileum where tone is lower and the waves are smaller and less frequent This gradient of motility in the small intestine is apparent in balloon recordings in human subjects and the diminution in rate of transit is observed in barium meal studies Moreover the level of tone is almost certainly the most important factor in limiting the distance that peristaltic rushes initiated by the act of swallowing can travel down the intestine Even when no contractions are demonstrable semi fluid contents continue to move forward providing the level of tone is favourable because transport depends upon a localized pressure gradient between any two immediately adjacent sections of gut and the fluctuations in the level of tone may *well be the determining factor For example simultaneous measurements* of intragastric and intraduodenal pressures have demonstrated that food passes out of the stomach only when the pressure in the antrum exceeds that in the duodenal bulb and this pressure gradient is dependent upon the tone *of the antrum and on* those contractions which travel right up to the pyloric sphincter and occlude the lumen as they progress (Quigley 1947)

Segmenting and peristaltic waves are frequently called non propulsive and pro pulsive contractions respectively but these terms are misleading because they imply specific effects on transport Although the barium is frequently seen to move forward in the small gut when a peristaltic wave appears on the graphic record (Fig 207) the correlation is by no means invariable and conversely the *barium continues* to move onward in the absence of peristaltic waves possibly by a process of progressive segmentation (McLaren and others 1950) Indeed the motility pattern in some subjects consists almost entirely of rapid low amplitude waves with *only occasional peristaltic waves (Chapman and others 1950a)* Moreover Alvarez (1948) has pointed out that the latter may pass on down the wall of the gut leaving the contents behind but these continue to flow on and eventually pick up a *new wave lower down*

In the colon the relationship between motility and transport is even more

obscure The passage of material from the ileum towards the hepatic flexure is not accompanied by any well defined muscular movements and the remainder of the colon shows no activity radiologically in the intervals between the very occasional mass movements and yet graphic records from balloons are similar to those of the small gut except that there are long periods of inactivity as in the stomach

NEUROMUSCULAR REGULATING MECHANISMS

Douglas (1949) noted that when a segment of jejunum was transplanted to the lower ileum in a dog its rate of rhythmic contraction fell to about that of the ileum and further investigations showed that the rate of contraction of the jejunum must be influenced by and co-ordinated with that of the duodenum so that they may act as a physiological unit as far as motility is concerned Some of the mechanisms responsible for co-ordination of this kind and for integrating motor activity throughout the whole length of the gut will now be considered

Myogenic activity

Although influenced by the nervous system tone and segmenting movements are dependent solely upon the rhythmical property of the muscle itself for they are not abolished when all nerve cells are either paralysed by drugs or completely stripped away from the muscle layers This rhythmic activity presumably depends upon the continuous release of acetylcholine in the wall of the digestive tract and the choline acetylase which is responsible for its synthesis does not originate mainly from the mysenteric and submucous plexus but is non nervous in origin (Feldberg and Lin 1950)

Reflexes and humoral mechanisms

Nervous reflexes of intrinsic and extrinsic origin and humoral mechanisms are constantly modifying this background of myogenic activity and thus retarding or propelling the intestinal contents in relation to the progress of digestion and absorption For example the motility of the stomach is stimulated by meals but gastric emptying is delayed in various ways until the consistency pH and osmotic pressure of the contents have been suitably adjusted Amongst the restraining influences which come into play are the transient inhibitory gastric feeding reflex adjustment of the tone of the stomach wall to the quantity and consistency of the food and depression of gastric motility by a full duodenum and by specific substances acting on the duodenal bulb Some of these substances such as acids and products of protein digestion exert their inhibitory effect through the enterogastric reflex and vagus nerve while others such as fats and sugars act by liberating enterogastrone The entry of food into the stomach may also initiate mass peristalsis in the colon through the gastro-colic reflex Similarly in the small gut motility is stimulated both by the act of swallowing which often starts a peristaltic rush and by increased pressure in the lumen which initiates the peristaltic reflex but as in the stomach restraining influences also come into play which increase intestinal tone and thus retard the passage of material to ensure adequate digestion and absorption Gregory (1950) has devised an ingenious method for

studying some of the factors in conscious dogs Some mechanisms operate through extrinsic reflexes which probably act through the vagus nerves and are initiated by both the act of swallowing and the presence of food in the stomach others are intrinsic reflexes which are not dependent upon extrinsic nerves The latter are local responses to the presence within the intestinal loop of fluid which either deviates appreciably from neutrality and isotonicity or contains substances such as protein digestion products or bile Like the peristaltic reflex these intrinsic reflexes are abolished by anaesthetization of the mucosa of the loop which suggests that they are dependent upon the intra mural plexuses this is of considerable interest as very little is known about the part played by these plexuses in regulating muscular activity To what extent conditions in different segments of the small gut influence motility in other segments under normal conditions is unknown but mechanical stimulation of one loop will initiate the intestino intestinal reflex and thereby inhibit tone and motility in another loop

Functions of extrinsic nerves

The current vogue of autonomic surgery for a wide variety of disorders has proved beneficial in only a few conditions but by providing opportunities for studying the effects of denervation in man it has helped to clarify the function of the vagus and sympathetic and thereby to define the therapeutic limitations both of surgery and drugs

Evidence from animal experiments—The relative importance of the regulating mechanisms is not clear but the extrinsic nerves have often been sectioned in animals without any permanent effect on motility or transport despite the fact that extrinsic reflexes are dependent upon them and that many local responses of the bowel wall are readily influenced by them Section of the vagi frequently results in a temporary depression of gastric motility while splanchnicectomy may augment intestinal motility and in general the vagus seems to exercise the greater influence on the stomach and the sympathetic on the intestine The effects of stimulation are unpredictable but seem to depend mainly upon the prevailing muscular activity of the bowel wall and sphincters at the time the vagus is pre dominantly motor and the sympathetic predominantly inhibitory The fact that stimulation or section of these nerves may have such contradictory and unpre dictable effects casts serious doubt on the traditional conception of constant antagonism between the two sections of the autonomic nervous system and seems to support Alvarez s view that both tend to inhibit excessive activity and spasm and through the external reflexes help to integrate the muscular activities of all parts of the gut

Sympathectomy and spinal anaesthesia—Abdominal symptoms are uncommon after lumbo dorsal sympathectomy and most experimental investigations have failed to demonstrate any significant changes in the motility of the stomach or intestines (Bingham and others 1950 Morlock and others 1950) The motility of the upper small intestine was studied in a group of 15 hypertensives on whom sympathectomy had been performed from 1 to 6 years previously and it was not possible to detect any deviations from the normal pattern in the balloon kymographic recordings (Rowlands and Sweet 1951) To test for the possible

regeneration of the nerves the balloon was rapidly distended with air but failed to produce pain in any of the patients whereas subjects with intact sympathetic nerves invariably develop pain when the pressure is suddenly raised to about 40 millimetres of mercury All these studies were on resting subjects and it may be argued that the effects of sympathectomy become apparent only under conditions of stress but there is no clinical evidence for this and it was found that intravenous injections of adrenaline had no greater effect on gut motility in patients after sympathectomy than in normal subjects Moreover in a few tests on normal subjects there has been no significant change in the motility of the upper small intestine during or after the performance of the cold pressor test for which the sympathetic constitutes the motor pathway the effects of stimulation by sympathomimetic drugs are also unimpressive

The effect of spinal anaesthesia is difficult to assess since any stimulating action is likely to be masked by the profound effects of morphine and scopolamine which are commonly administered pre operatively Helm and Ingelfinger (1944) recorded motility with balloons before and during 11 abdominal operations and found no change following the spinal anaesthetic but all their patients had received pre operative medication

Thus the sympathetic pathways in man do not appear to exert a continuous inhibitory effect on gut motility as they do in some animals but it is possible that adrenergic overactivity is a factor in some pathological conditions such as the ill defined syndrome of neurogenic intestinal obstruction or neurogenic ileus since spinal block is said to cause an increase in propulsive contractions and to improve co ordinated bowel activity in some cases of this kind Sarnoff and others (1948) emphasize the importance of withholding pre operative medication when investigating the efficacy of spinal block in such cases and suggest that the masking effect of the drugs may explain the disappointing results reported by some surgeons

Vagotomy.—In contrast to the unimpressive effects of sympathectomy profound motor disturbances frequently follow vagotomy Balloon kymographic recordings and radiological studies after complete vagotomy often reveal an atonic stomach with complete absence of peristaltic activity and gastric retention may be so severe that choline esters have to be used to stimulate contractions and promote emptying For this reason some surgeons have preferred to combine vagotomy with some other procedure such as gastro-enterostomy However the motor inactivity like the secretory changes is temporary and symptoms associated with gastric retention usually disappear spontaneously after a few months Spasm of the pylorus has been reported and transient dysphagia sometimes occurs In contrast to these effects on gastric function most studies of small intestinal motility have shown no change after vagotomy and the delay in the passage of barium which has often been noted is usually attributed to the slow emptying of the stomach On the other hand diarrhoea is a common post-operative symptom and it is interesting that hyper irritability of the bowel has often been described in animals after vagotomy The extent of the motility changes in the stomach is not directly related to the completeness of the vagotomy and therefore cannot replace the insulin test as an index of this since gastric atony may occur when the vagus nerves have been intentionally only partially severed (Weinstein and Hollander 1950)

Role of the central nervous system

That gastro intestinal disturbances often accompany emotional stress has been recognized for centuries but there is now experimental evidence that particular emotional states may be associated with specific changes in the motor and secretory activities of the salivary glands oesophagus stomach and colon Certain emotional conflicts such as unexpressed anger resentment and suppressed hostility are often accompanied by hypermotility of the stomach and colon while fear and depression tend to induce hypomotility (Wolf and Wolff 1947 Grace Wolf and Wolff 1950) Moreover Wolf (1950) has demonstrated that the influence of emotional disturbances may be so intense that the usual pharmacological effects of drugs such as atropine on the motility of the stomach and colon may be nullified or even reversed

Some advance has been made in defining the nervous pathways which connect the brain and bowel Stimulation of the anterior and medial parts of the hypo thalamus in monkeys causes increased peristalsis in the stomach providing the vagi are intact while stimulation of the posterior and lateral aspects abolishes motility Babkin (1950) could find only two points in the cerebral cortex of the dog which on being stimulated had an effect on the motility of the antrum These were the orbital surface of the frontal lobe and the anterior end of the cingulate gyrus the usual effect was inhibitory but motility was occasionally increased by stimulation of the orbital surface He found that antral contractions were in creased both by ablation of the cingulate gyrus and by removal of the hypothalamus by suction Babkin s interpretation of these findings is that the cortical areas usually exert a moderating influence on the parasympathetic centres in the hypo thalamus which in turn restrict the activity of the vagal centres in the medulla but that positive impulses from the cortex or hypothalamus may increase the activity of the vagal centres in the medulla Thus he postulates the vagus nerves as the main pathways from cortex to stomach both for inhibitory and excitatory impulses and adduces considerable evidence that abolition of gastric motility is due to depression of the lower vagal centres in the hypothalamus and medulla by inhibitory cortical impulses rather than to stimulation of sympatho adrenal centres while increased motility results from removal of the moderating influence of the cerebral cortex and not from depression of the sympathetic innervation

These conclusions are based on experiments on animals but there is some evidence in man that the vagus nerves carry the efferent impulses concerned in the production of gastric hyperfunction in response to threatening life situations (Wolf and Wolff 1947) Gastric hyperaemia and hypermotility occurred when feelings of anger and resentment were induced in a patient prior to vagotomy but after the operation these emotional conflicts were not associated with changes in gastric function Both pylorospasm and hypermotility have been reported after frontal lobotomy and Penfield has recently obtained evidence in man of a sensory and motor representation of the alimentary tract in the island of Reil

EVALUATION OF THE ACTIONS OF DRUGS ON MOTILITY

So little is known about the factors influencing the motor activities of the human gut that the physiological disturbances underlying many of the commonest gastro intestinal symptoms are quite obscure but the clinician must adopt some working

hypothesis and choose his therapeutic agents accordingly The clinical usefulness of a drug cannot be inferred from its pharmacological actions in animals but on the other hand therapeutic trials are notoriously difficult to control adequately some objective method of assessment should therefore be used whenever possible Although the techniques available for recording motility are crude they can provide important information about the effects of drugs but even objective methods of this kind may give fallacious results and in fact different workers using a variety of recording techniques have sometimes ascribed opposite effects to the same drug Some of these differences are only apparent and are clearly due to the inexact use of descriptive terms but many fallacies have arisen because spontaneous variations in motility have been interpreted as effects due to the drug being tested Errors of this kind are especially common when assessing drugs given by mouth and can be avoided only by making prolonged recordings prior to the administration of each drug and by studying the fluctuations in motility following placebos Moreover the majority of tests have been made on the stomach or colon where the contractions occur in irregular unpredictable sequences separated by prolonged periods of quiescence where the relationship between motility and transport is especially obscure and effects due to suggestion are extremely difficult to control The validity of many of these studies is further impaired because the recording balloons were introduced through ileostomies or colostomies in patients suffering from a variety of diseases

To obtain reliable results with balloon techniques the following conditions should be fulfilled and particularly when testing drugs given by mouth

(1) The recording system must be sufficiently sensitive to register slight changes in tone and must be standardized as far as possible for each test
(2) Similar areas of gut should be studied in each test and preferably the duodenum and upper jejunum as these have well developed and sustained motility patterns
(3) Healthy volunteers should be trained as subjects and only one drug should be tested on any one day
(4) Spontaneous fluctuations of motility should be studied in each subject over a period of 5 6 hours before and after the administration of placebos
(5) Every effort should be made to exclude the effects of suggestion
(6) Drugs should be given by the usual route and in the doses commonly employed therapeutically
(7) Simultaneous records from two or more balloons placed in adjacent segments are desirable

Effects of placebos on motility

With the above considerations in mind 14 studies of the variations in the motility patterns of the duodenum and upper jejunum in 12 healthy subjects were made (Chapman and others 1950a) Continuous recordings were made on a kymograph from 4 balloons placed at intervals of 4 inches apart with the most proximal in the antrum of the stomach The size shape and volume of the balloons were standardized and the sensitivity of their respective recording systems was checked before intubation The subjects reclined comfortably with abdominal muscles relaxed and after an initial period of recording lasting about an hour they were given an inert tablet to swallow or a subcutaneous injection of water

and the recording was continued for a further period of about 4 hours Measurements with a polar planimeter of the surface areas representing tone and total contractions respectively provided a more quantitative analysis of the tracings

Slight fluctuations of tone occurred at frequent intervals and the level was often observed to rise above the base line in one balloon at the same time as it fell below it in an adjacent balloon Very pronounced but transient elevations occurred either once or twice in the course of 8 of these studies (Fig 208) These 'spasms' were characterized by a sudden rise in tone to the level of the peaks of the highest peristaltic waves where it remained for 5–16 minutes and then fell rapidly to its

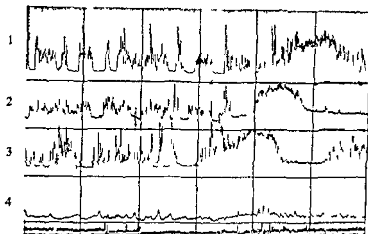


FIG 208 —Graphic record showing a 'spasm' passing down the gut Vertical lines indicate time at 5 minute intervals Horizontal lines are the base lines of each balloon Tracing number 1 is from the upper jejunum 2 from the third part of the duodenum 3 from the second part and 4 from the antrum which is in a quiescent phase

original level They always appeared first in the tracing of the most proximal balloon and passed rapidly down the intestine to appear successively in the second, third and finally in the most distal balloon They were not associated with symptoms of any kind and could not be attributed to the placebo since in some of these and in other studies they appeared before the medication was given

Peristaltic waves decreased as the level of tone was rising and disappeared entirely when a spasm had fully developed and did not return for periods varying from 5 to 60 minutes after the spasm had ended They also showed slight fluctuations independently of spasms and in most of the subjects they had decreased by about 30 per cent at the end of the recordings

Segmenting waves appeared to show less variation and to be more persistent than the peristaltic waves but it was not possible to assess them in a quantitative manner

A specific pattern of motility usually recurred in all tests on any given individual and this characteristic pattern made it easier to assess the significance of minor variations of motility following drugs

Effect of suggestion —The possibility that the variations in motility which were

observed were due to the effect of suggestion associated with the administration of the placebo was considered but similar changes occurred just as frequently during the control period preceding the medication Moreover it was not possible to correlate any subject s apparent or expressed dislike of the procedure with variations in the motility pattern This is surprising in view of the striking changes in motility both of the stomach and colon that have been demonstrated in association with emotional stress For although these tests were deliberately planned to minimize the effect of suggestion there is no doubt that the presence of a four channelled tube lodged intranasally for many hours after somewhat unceremonious manipulations during repeated fluoroscopy will engender feelings of resentment hostility and even anger from time to time in most starving subjects and particularly when they are kept in a supine position for prolonged periods However it is said that colonic motility is disturbed by emotional strain only when the subject believes his personal security to be threatened and it seems unlikely that this condition obtained in these subjects On the other hand it may be that the more complex and sustained muscular activities of the small intestine are less susceptible to emotional stress than the simpler intermittent motility of the stomach and colon Clinical experience would seem to support this view for whereas few would deny the significance of emotional factors in the dyspepsias associated with disturbances of gastric function and in colitis similar syndromes due to disorders of the small gut are rarely encountered

MODIFICATION OF MOTILITY WITH DRUGS

Some clinicians believe that spasm at the sphincters or elsewhere in the gut is the main cause of symptoms while others attribute them to dysynergia between adjacent functional segments of bowel (Posey and others 1948) or to anti peristalsis but the main objectives of treatment with drugs are to relieve pain or discomfort and to hasten or retard the passage of intestinal contents Difficulties arise however because a drug may relieve some symptoms only to replace them by others of a gastro-intestinal or more general nature and because the patient s prevailing emotional state may profoundly modify the action of the drug Thus it seems more profitable to review the actions of drugs as observed in experim ntal tests on human subjects rather than discuss their fundamental pharmacolog cal properties To avoid confusion it is emphasized again that the terms motility and transport are not synonymous and stimulation of motility may actually delay transport that foodstuffs and drugs may influence the passage of intestinal contents by virtue of their effects upon intestinal secretions and absorption and finally that the use of most drugs is limited by their side-effects on organs other than the gastro intestinal tract

Drugs which depress motility

Belladonna alkaloids—The actions of spasmolytic drugs were assessed by comparing them with placebos on the one hand and with the belladonna alkaloids on the other since the latter undoubtedly depress motility in the stomach and intestines when given by injection It was found in tests on 14 subjects that single therapeutic doses of either atropine or tincture of belladonna wh n given by mouth

either abolished or greatly reduced the peristaltic waves and that the maximum effect was reached in about 75 minutes but tone was not significantly reduced (Chapman and others 1950b) similar results are reported by Posey and others (1948) using patients with ileal or colonic stomas Although scopolamine is said to have a weaker peripheral action than atropine it was found that doses of 0 4 milligram subcutaneously had effects comparable to those of 0 6 milligram of atropine and it abolished motility and relieved symptoms in one patient after atropine had been repeatedly and unaccountably found to have no effect

The discrepancy between the impressive actions of this group of drugs in tests and their limited efficacy as spasmolytic agents in clinical practice is difficult to explain but limitation of dosage due to their unpleasant side effects is probably the most important factor Although the usual clinical doses were effective in the tests on normal subjects it is reasonable to suppose that much larger doses would be necessary to counteract hypermotility and spasm in patients Moreover the abolition of spasm is a much more effective therapeutic property than the depression of contractions but even in normal subjects their effect on tone when given by mouth was negligible It has been suggested that atropine may easily inhibit the acetylcholine upon which the rhythmic activity of intestinal muscle depends but it is known that very large doses are necessary to block the gastro intestinal branches of the vagus completely It follows that ideally these experimental tests should be made on hypermotile spastic intestines in patients but this is not practicable and it is questionable whether spasmogenic drugs such as morphine create conditions in any way analogous to those occurring in clinical disorders Butsch and others (1936) in experimental studies on patients who had tubes inserted into the common bile duct for biliary drainage induced spasm of the sphincter of Oddi with morphine and found that atropine would not relax it

Nitrites —These drugs have a powerful spasmolytic action in ordinary therapeutic doses and will relax the sphincter of Oddi rendered spastic by morphine but their action is much too transient and attended by too many side effects for general clinical use

Papaverine —This opium alkaloid has a much feebler spasmolytic action than the nitrites and is said to have no effect on the human intestine except when administered intravenously

Sympathomimetic drugs —These have a tendency to depress motility but their effects are very slight and transient A comparison was made of the effects of adrenaline on motility in a group of normal subjects a group of patients after sympathectomy for hypertension and a further group on whom coeliac ganglionectomy had been performed in addition to lumbo dorsal sympathectomy and splanchnicectomy increasing doses were injected intravenously starting with 5 micrograms A very slight transient depression of motility was observed in a few cases after very large doses and the different groups showed no significant difference in this response (Rowlands and Sweet 1951) The spasmolytic actions of ephedrine and amphetamine in ordinary doses are said to be very slight and unpredictable

Ganglion blocking drugs —Several quaternary ammonium compounds which paralyse the transmission of impulses in autonomic ganglia have the effect of depressing motility Many experimental studies have shown that the action of

tetraethylammonium on motility in man is similar to that of large doses of atropine given parenterally but it is ineffective by mouth and unsuitable for routine clinical purposes owing to its unpleasant and often alarming side-effects Intramuscular hexamethonium (C6) is said to inhibit gastric motility (Kay and Smith 1950) and delay gastric emptying and in some preliminary studies we have found that it depresses the motility of the duodenum There are no reports of experimental studies of its effect on motility when given by mouth but it tends to cause constipation and there is a report of severe ileus following its administration orally for 10 days (Bourne and Hosford 1951) Unfortunately this compound also causes undesirable side effects amongst which postural hypotension is often troublesome However there is some hope of obtaining compounds which will exert their effects almost exclusively on those ganglia which influence intestinal functions since the autonomic ganglia show a gradation in their sensitivity and this seems to vary with each ganglion blocking agent (Paton 1951) Moreover in addition to their ganglion blocking properties many of these compounds have direct actions on effector organs and these may enhance their value for particular purposes such as the inhibition of gut motility Thus Banthine which is being intensively studied in the United States of America has an atropine like action in addition to its ganglion blocking effect and many investigators have found that it is much more effective than atropine in depressing the motility of the stomach and intestines and is very much less toxic (Longino and others 1950) Another promising feature of these drugs is that it may be possible to adjust the dosage so as to diminish over activity of an organ before interferring with normal function as there is evidence that hexamethonium for example is more effective in blocking ganglia when they are transmitting more impulses than normally (Paton 1951)

Synthetic anti spasmodics—The members of this group are not necessarily related chemically but all were introduced as spasmolytic agents because they were found to be more effective than atropine when tested on strips of intestine and in animals and yet to be almost free from its unpleasant side-effects Most of them are said to have a direct depressant action on smooth muscle in addition to being anti-cholinergic and some of them also possess local anaesthetic properties Some of them were tested on the upper small intestine and it was found that Syntropan Pavatrine Asymatrine and Trasentine had either no effect or only an equivocal transient depressant action when compared with the belladonna alkaloids (Chapman and others 1950c Rowlands and others 1950b) Earlier favourable reports of the spasmolytic effects of some of these drugs on the human colon have not been confirmed by more recent studies Moreover it is notorious that initial clinical enthusiasm for so-called anti spasmodics is usually evanescent A really effective spasmolytic must presumably cause paralytic ileus but the ideal drug should exert its effect only upon abnormally spastic segments of gut and do so without causing unpleasant side-effects

Analgesic drugs

Barbiturates—It was found that Sodium Amytal given intravenously had no significant effect on motility and Posey and others (1948) noted no effect from phenobarbitone given by mouth there is no evidence that barbiturates enhance

the spasmolytic properties of other drugs Nevertheless these drugs are unquestionably more useful in the routine treatment of the dyspepsias than any anti spasmodic agent

Morphine —It is generally agreed that morphine retards the passage of material through the alimentary tract but conflicting views are held regarding its effect on motility Doses of 10 milligrams were given subcutaneously to 9 healthy subjects and changes in motility occurred after about 10 minutes throughout the whole period of subsequent recording which averaged 210 minutes tone was greatly increased due to intermittent spasms which recurred about every 15 minutes and peristaltic waves were almost completely abolished (Rowlands and others 1950a) An initial increase in peristaltic waves was not observed nor was a prolonged period of atony following an initial severe spasm in the duodenum (Abbott and Pendergrass 1936) The effects on the colon are similar to those observed in the small gut (Adler and others 1942) Constipation would seem inevitable in the absence of peristaltic contractions associated with an increase in tone which at times must almost or completely obliterate the lumen Although these actions of morphine are useful in the treatment of some conditions they usually constitute undesirable side effects when it is used for the relief of severe abdominal pain

Whether it should be used for the prophylaxis or treatment of paralytic ileus is a vexed question but there is no doubt that many surgeons believe that it is beneficial Burn in his textbook (1948) condemns its use in vehement terms and cites the idea that morphine might increase the movements of the intestine as a good example of the complete neglect of pharmacological teaching and of evidence which has been established as complete for many years In fact the literature on the subject is a classical example of contradictory statements and of confusion due to the bewildering variety of experimental techniques employed in animals and to the lack of standardization in terminology the only certain fact that emerges is that morphine induces constipation and this is a clinical observation which requires no experimental support Clinicians might well be excused for believing that it increases the movements of the intestine since some pharmacologists refer to its effect in increasing intestinal tone as a stimulating effect on intestinal motility Burn bases his argument upon the results of experiments in animals but the fallacy of supposing that the clinical usefulness of drugs which influence the motor functions of the gut can be determined from their pharmacological actions in animals is becoming increasingly evident Burn himself provides another example when he advises the use of pethidine or papaverine for the relief of pain after operations on the biliary passages because unlike morphine they are spasmolytics The fact is that pethidine was introduced as a spasmolytic drug in 1939 but experimental observations in man have shown that it increases tone in the biliary tract and to a lesser extent in the small gut (*vide infra*) papaverine has only a very feeble and brief spasmolytic effect in man Pharmacological properties should not be the final criterion in selecting the best drug for the relief of a disorder involving the motor functions of the gut and more particularly in a condition like paralytic ileus where the aetiological factors and pathology are so varied and usually so obscure It is possible that the action of morphine in increasing intestinal tone might be valuable

and its other properties may be indispensable in some post operative cases However as there is now considerable agreement about the results of exp ri mental studies in man and as these confirm the clinical view that it is by no means an ideal drug for the treatment of paralytic ileus it would seem reasonable to give extended trials to drugs such as DFP which judging from experimental studies in man possesses stimulating properties which would be more useful in this disorder (*vide infra*) That some surgeons still use morphine in liberal doses as the drug of choice in all cases of ileus is indeed surprising

Morphine substitutes—A spasmolytic drug with the analgesic properties of morphine would be very useful in the treatment of pain due to smooth mu cle spasm Many drugs have been tested on the small intestine and biliary tract in man including codeine morphine derivatives such as Dilaudid and Metopon and the synthetic substitute Amidone (Methadone Physeptone) Some of these caused rather less spasm than morphine but the difference was too slight to be of any clinical significance (Gaensler and McGowan 1950)

Pethidine (*Demerol*)—This drug is related chemically to atropine and was originally introduced as a spasmolytic agent It is said to reduce the tone of the intestinal musculature in man but the evidence is unconvincing The effect of 100 milligram doses subcutaneously in eight subjects was studied It decreased peristaltic waves to about the same extent as morphine but for a much shorter period of time so that they began to reappear after about 100 minutes Inter mittent spasms also occurred but very much less frequently than after morphine (Chapman and others 1950d) Thus although it was not spasmolytic it was much less spasmogenic than morphine and its effect on peristaltic waves was less prolonged Gaensler and others (1948) studied its effects in patients after choledochostomy and found that it cau ed spasm of the sphincter of Oddi and increased intrabiliary pressure almost as much as morphine did Williams and Streeten (1950) using a new technique in conscious dogs found that morphine and Amidone had a marked inhibitory effect on the propulsive power of the intestine whereas pethidine did not interfere with propulsion Thus its beneficial effect is probably due to its central sedative action and not to any peripheral spasmolytic effect but unlike morphine it does not appreciably retard transport on the other hand it is a much less potent analgesic

Drugs which stimulate motility

Choline esters—Mecholyl (acetyl β methylcholine) has been reported to have a brief but often intense stimulating action but it was found that 12 milligram doses subcutaneously had only a slight effect on motility although unpleasant subjective reactions were common Urecholine (carbaminoyl β methylcholine) is the most useful and least toxic of this group of drugs and has been useful in restoring gastric motility and relieving stasis in patients after vagotomy

Pituitrin—Many conflicting statements have been made about the effect of this drug on motility but its principal action in man seems to be a brief stimulation of peristaltic waves with little or no effect on tone It was the most valuable drug tried by Alstead and Patterson (1948) for increasing the output of flatus from the bowel

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Rowlands E. N Chapman W P Taylor A and Jones C M (1950a) *Surg Gynec Obstet* 91 179
— — — — (1950b) *Ibid* 91 513
Sarnoff S J Arrowood J G and Chapman W P (1948) *Ibid* 86 571
Weinstein V and Hollander F (1950) *Gastroenterology* 14 586
Williams E M V and Streeten D H P (1950) *Lancet* 2 213
Wolf S and Wolff H G (1947) *Human Gastric Function* 2nd ed New York Oxford University Press
— (1950) *J clin Invest* 29 100

Anti cholinesterases—Neostigmine (Prostigmin) intramuscularly stimulates motility in both the small and large intestines its action is said to be potentiated by Pitressin and ergotamine Unlike the choline esters it is not effective in promoting gastric emptying after bilateral vagotomy

Di isopropylfluorophosphonate (DFP) has a more prolonged action since it causes an irreversible inactivation of cholinesterase but like neostigmine its effect on the gut is antagonized by atropine Grob and others (1947) found that intramuscular injections produced a marked increase in motility of the small and large gut and after a single injection the gut was sensitized for 1-3 weeks to the stimulating actions of neostigmine morphine and vasopressin It was found to be very effective in 64 cases of abdominal distension due to various causes but in the more severe cases repeated injections were necessary and neostigmine or vasopressin were sometimes given after the DFP Quilliam and Quilliam (1949) consider that it is a more valuable drug in the treatment of post operative paralytic ileus than either neostigmine or posterior pituitary extract

REFERENCES

Abbott W O and Pendergrass E P (1936) *Amer J Roentgenol* 35 289
Adler H F Atkinson A J and Ivy A C (1942) *Arch intern Med* 69 974
Alstead S and Patterson J F (1948) *Lancet* 1 437
Alvarez W C (1948) *An Introduction to Gastroenterology* 4th ed London Heinemann
Babkin B P (1950) *Edinb Med J* 57 419
Bingham J R Ingelfinger F J and Smithwick R H (1950) *Gastroenterology* 15 6
Bourne G and Hosford J (1951) *Lancet* 1 527
Brody D A and Quigley J P (1947) *Gastroenterology* 9 570
Burn J H (1948) *The Background of Therapeutics* London Oxford University Press
Butsch W L McGowan J M and Walters W (1936) *Surg Gynec Obstet* 63 451
Chapman W P Rowlands E N Taylor A and Jones C M (1950a) *Gastroenterology* 15 341
— — and Jones C M (1950b) *New Engl J Med* 243 1
— — — (1950c) *J Amer med Ass* 143 627
— — — (1950d) *New Engl J Med* 243 171
Douglas D M (1949) *J Physiol* 110 66
Feldberg W and Lin R C Y (1950) *Ibid* 111 96
Gaensler E A and McGowan J M (1950) *Gastroenterology* 16 484
— — and Henderson F F (1948) *Surgery* 23 211
Grace W J Wolf S and Wolff H G (1950) *Gastroenterology* 14 93
Gregory R A (1950) *J Physiol* 111 119
Grob D Lilienthal J L and Harvey A M (1947) *Johns Hopk Hosp Bull* 81 245
Helm J D and Ingelfinger F J (1944) *Surg Gynec Obstet* 79 553
Kay A W and Smith A N (1950) *Brit Med J* 1 460
Longino F H Grimson K S Chittum J R and Metcalf B H (1950) *Gastroenterology* 14 301
McLaren J W Ardran G M and Sutcliffe J (1950) *J Fac Radiologists* 2 148
Morlock C G Hightower N C Code C F and Craig W M K (1950) *Gastroenterology* 16 117
Paton W D M (1951) *Brit Med J* 1 773
Penfield W (Lane Lectures) quoted by Babkin B P (1950) *Gastroenterology* 14 479
Posey E L Bargen J A Dearing W H and Code C F (1948) *Gastroenterology* 11 344
Quigley J P (1947) In *Medical Physics* ed by O Glasser Chicago Year Book Publishers
Quilliam J P and Quilliam T A (1949) *Lancet* 1 603
Rowlands E N and Sweet W H (1951) To be published

of the family It can be stated unequivocally that the colon neuroses do not pre dispose to ulcerative colitis and that the type of immature personality recognizable in certain cases is in no sense a specific one

AETIOLOGY

Ulcerative colitis is the bacteriologist s bugbear The routine examination of many thousands of specimens of stools or material obtained direct from the ulcerated surface has failed to identify any specific organism Very occasionally a pathogen of the typhoid paratyphoid dysentery group is isolated to justify a monotonous and usually unremunerative procedure More commonly an excess of enterococci or β haemolytic streptococci are grown but none has yet been shown to have other than secondary significance It may be added that there is as yet no evidence to suggest that the disease is due to a virus infection though this field has by no means been fully investigated

In the search for other aetiological factors many fields have been explored none more diligently than the psychological background of the patient The effect of the emotions on alimentary function has long been recognized The well known work of Wolf and Wolff (1943) on the stomach has been paralleled by similar observations on the human colon in 4 fistulous subjects (Grace and others 1950) and Wright and Florey (1938) showed that the effect of stimulating the sacral division of the parasympathetic nerves the nervi erigentes in cats was an increase in muscular activity in vascularity and in the secretion of mucus Lium and Porter (1939) and more recently Wener Hoff and Simon (1949) using dogs have shown that long continued stimulation by various methods including cholinergic drugs leads to intense colonic engorgement haemorrhage and ulceration thus paving the way for further injury and secondary invasion It is tempting to regard the local re action of the colon in ulcerative colitis as the result of long-continued over stimulation of the parasympathetic nerves particularly the sacral outflow which supplies the distal colon and rectum but if we accept this as a common pathway in ulcerative colitis it is difficult to explain why cases of muco-membranous colic a functional disorder now practically extinct and its modern and milder prototype colon neurosis both clear examples of colon over activity have not led to the major disease

In any long-continued illness particularly an abdominal illness emotional reactions are common and play their part in the perpetuation of symptoms The colon neuroses afford good examples and attacks and relapses of ulcerative colitis may be occasioned by upheavals in the life situation but there is also much evidence to suggest that emotional instability can be recognized before the onset of the colitis Wittkower (1938) came to the conclusion that ulcerative colitis was a disease of the mentally ill or maladjusted almost all his series showing characteristic disorders obvious neuroses or psychoses In most of the patients studied psycho logical abnormalities far beyond the range of individual differences in the average population were found to antedate the initial onset of the colitis The chief feature of these patients is their immaturity many appear to be dependent feeble personalities seeking protection from their environment and often abnormally attached to one or other parent Over-conscientious sensitive natures are common scrupulous cleanliness and tidiness to the point of fussiness are frequent traits

CHAPTER 23

ULCERATIVE COLITIS

T L Hardy and B N Brooke

The following article does not claim to give a full account of ulcerative colitis in all its aspects but endeavours to focus attention on those aetiology and treatment in particular which have assumed prominence in recent years Ulcerative colitis or colitis gravis is a non specific disorder of the colon which can be traced back in medical history as far as 1669 when Sydenham described the bloody flux According to Hurst (1921) it was first separated from bacillary dysentery by Wilks and Moxon (1875) although Hurst himself maintained for many years that it was in fact a sporadic and chronic form of bacillary dysentery It is now however realized that the two disorders are alike only in their pathological end results It is a grave disorder with a high mortality affecting principally young people in the formative and creative years of life and often those more intelligent and more sensitive than their fellows It runs a long course with pronounced tendency to relapse and despite much patient investigation and the steady accumulation of knowledge of its various aspects remains obscure in its aetiology uncertain in its course and unreliable in its response to treatment

Age and sex

The disease is one of adult life particularly young adult life the great majority 70–80 per cent of cases occurring between the ages of 20 and 40 years The disease is rare after 50 years and according to most writers very rare in childhood though Jackman and others (1940) gave a good review of 95 children met with in a total group of 871 patients with this disease

There is no significant difference to be found in sex incidence

Mortality

It is difficult to obtain reliable mortality figures for the Registrar General s returns include ulcerative colitis under one of two headings colitis and ulceration of the intestine while similar uncertainties in classification invalidate most hospital statistics All observers agree that the mortality is high and especially high in the year of onset Rice Oxley and Truelove (1950) report that 22 per cent of a series of 121 cases died within a year of the onset of their disease and that about one third were dead at the end of 5 years

Personal and family history

There seem to be no predisposing factors in this disease which usually appears from a clear sky and it is quite exceptional for it to occur in more than one member

the presence of a mucinase which does attack mucus and is present in the faeces in ulcerative colitis but not in normal stools It does not appear to be associated with bacteria found in the faeces and has been shown to be present after penicillin streptomycin or aureomycin therapy all of which cause a progressive decrease in lysozyme titre There seems to be some correlation between mucinase and proteolytic activity in the faeces in ulcerative colitis Its significance is being investigated

Summary

Experience and evidence suggest that ulcerative colitis is like peptic ulcer a disease of stress or stresses which varying in importance from case to case produce a common end result in a colon predisposed or conditioned to abnormal reaction Emotional episodes occurring in an immature personality seem important and it is possible that some combination of psychoneurotic traits or some specific type of conflict as suggested by Groen (1947) may prove to have significance Respiratory and other infections such as amoebic dysentery may play a part while secondary infection intensifies a local reaction which ultimately becomes irreversible The nature of this reaction and its localization to the colon remain obscure but may be the result of factors which interfere in some way with the protective properties of mucus Whatever be the outcome of these studies there clearly remain problems to be solved at several biological levels the local cellular mechanism the functional integrity of the colon as an organ the nervous and other pathways and higher centres the individual and his reaction to the society in which he lives

THE INFLUENCE OF PREGNANCY

Few studies have been made of the effects of pregnancy on ulcerative colitis but these tend to show that pregnancy *per se* has little effect on the disease In fact Felsen and Wolarsky (1948) report that in over half of 34 patients studied the colitis was definitely improved Tumen and Cohn (1950) make the important point that pregnancy itself has little influence but that pregnancy occurring in emotionally immature women who are not prepared psychologically for marriage and parenthood may be associated with ulcerative colitis or its relapse and this certainly accords with the writers experience Ulcerative colitis in remission or even in a mildly active phase need not be considered a barrier to pregnancy but advice concerning this must be based on a psychological as well as a physical assessment in each individual

ONSET AND DIAGNOSIS

The onset is usually gradual sometimes abrupt only rarely is it fulminating The first symptom is generally a watery diarrhoea appearing in an individual with previously normal bowel function Pus cells and red blood cells are present on microscopic examination Mixed blood and pus in visible form appear later Occasionally important bleeding occurs at the onset and when this is associated with haemorrhoids the true nature of the condition may be overlooked Pain as an early symptom is unusual

They approach with anxiety and assume with trepidation the responsibilities and implications of adult status Marriage is fraught with uncertainty and sexual maladjustments are frequent It should be noted however that these features do not constitute in any sense a specific personality but are rather the familiar material of the psychiatrists consulting room (Hardy 1945)

On the other hand Sloan and others (1950) from a study of the records of 2 000 cases seen at the Mayo Clinic were not impressed either with the neuroticism of the patients or the role of emotional disturbances in relation to the aetiology of the disease They attribute a greater importance for example to catarrhal infections It is however fair to point out that this series covers a period from 1918 to 1937 in the earlier part of which the role of the emotions had not been the subject of careful study Again as Paulley (1950) points out unusually detailed histories and often more than one interview are required before a psychological assessment can be said to be complete It is impossible to establish yet any degree of accuracy or statistical computation in these matters as we lack a standard of measurement but it would be as wrong to ignore the evidence as to regard ulcerative colitis as a psychosomatic disorder without qualification One cannot disregard the fact that other forms of stress particularly respiratory infections will at times precipitate a relapse in ulcerative colitis and the disease occasionally follows in the wake of amoebic dysentery (Stewart 1950)

Although certain stimuli or stresses seem to be important in precipitating the disease we are far from understanding the factors which determine a continuous type of reaction or its localization in the colon Some have attributed it to allergy but the evidence is far from convincing allergic reactions are not conspicuous either in the patients themselves or their relatives Bockus (1944) suggests that the Schwartzman phenomenon a non specific immunity response may account for the recurrent attacks

Lysozyme

The colon in man is more subject to trauma than any other part of the alimentary canal and this applies particularly to the distal colon and rectum where the faeces are normally solid or semi solid and the great majority of cases of ulcerative colitis have their origin There is a generous provision of mucus secretion which is normally absorbed but under conditions of irritation and infection may be passed in the stools in large quantities It has been suggested that the physical properties of mucus are in some way impaired by enzyme action and lysozyme an enzyme first isolated by Fleming and Allison (1922) has been cited as an important agent It occurs in many bodily secretions notably the tears the bile and the saliva Egg white is an important source and so is pus Lysozyme is present in considerable quantities in the stools in ulcerative colitis and varies directly with the severity of the disease There is however no experimental evidence to show that it has any action on mucus as secreted by the stomach or colon either obtained indirectly through a gastric tube or in the faeces or directly from a gastric or colonic fistula (Glass and others 1950) Sammons (1951) has found that the lysozyme of the stools in ulcerative colitis varies directly with the amount of pus present and is probably derived from this source It was not present in a controlled series of cases of diarrhoea where pus was absent Further Sammons has reported



Fig 11 —Barium enema ulcerative colitis advanced disease showing ulceration



Fig 212 —Barium enema ulcerative colitis advanced disease



FIG. 209.—Barium enema: ulcerative colitis, early stage.



FIG. 210.—Barium enema: ulcerative colitis, advanced disease.

disappears the colon is shorter narrower and much less distensible (Fig 210) and the margins may be ragged with the contours of shallow ulcer craters in severe cases (Fig 211) In the final phase the colon is reduced to a contracted fibrous tube with complete loss of function (Fig 212) In some cases about 10 per cent healing is established with the regeneration of islands of mucous membrane producing the condition of pseudopolyposis (Fig 213)

COURSE AND PROGNOSIS

The course of ulcerative colitis is prolonged and unpredictable The fluctuations from week to week are remarkable and there are few diseases where the clinical picture can alter for better or for worse with such rapidity During convalescence although some degree of colon function may be re established as shown by a tendency to formation of the stools and an occasional improvement in the opaque enema pictures the persistence of the disease in the rectum is noteworthy Many still show active inflammation some are congested and bleed readily when swabbed Others show narrowing with stricture formation and an atrophic type of mucous membrane while more may show pseudopolypoid changes Nevertheless it is surprising how many are capable of leading useful lives though of course at some hazard Rice Oxley and Truelove (1950) report that about 40 per cent of their cases were leading near normal lives 50 per cent lives of some restriction and 10 per cent were totally incapacitated

Complications

Local complications —The local complications of ulcerative colitis are numerous one or more occurring in 35 per cent of all cases (Sloan and others 1950) Most of these are the direct result of the disease process stricture especially stricture of the rectum is common in fact some degree of narrowing of the rectum is almost inevitable in long standing cases and is one of the local conditions which may ultimately call for ileostomy Fissures ulcers and fistulae round the anus including recto vaginal fistulae are relatively common and add much to the patient s dis comfort They are very intractable to treatment and again may need ileostomy and even colectomy before full healing takes place Polyposis or pseudopolyposis for the polyps are inflammatory in origin is hardly a complication but rather an inadequate attempt at healing

Carcinoma —This complication calls for special notice and longer experience makes it quite clear that carcinoma of the colon occurs with greater frequency in ulcerative colitis than in the population normally at risk The published incidence varies with different authors from 3 to 6 per cent of all cases but in view of the varying severity of the colitis and the difficulty in making a firm diagnosis of malignancy this is probably a conservative figure Certain distinctive features of malignant disease supervening in ulcerative colitis can now be recognized (1) it occurs in subjects at a relatively early age the chief incidence lying between 30–39 years (Sloan and others 1950) (2) it occurs only after the colitis has been estab lished for some years the average lying between 5–9 years (3) it shows a high degree of malignancy and a tendency to metastasize early and (4) it may be multiple These are disturbing facts emphasizing the need for a very careful

The diagnosis is rarely in doubt the age the history of remission and relapse the flat and slightly tender abdomen the typical stools the occurrence of anaemia and dehydration make up a characteristic picture Irregular fever may or may not be present Confirmation can be readily obtained by proctoscopy for cases in which the rectum is normal throughout are quite exceptional Sigmoidoscopy and barium studies are best avoided during the acute phase but are of great value when this is past

Radiological diagnosis

The progress meal and the opaque enema should each be used the progress meal *consisting of skiagrams taken frequently in order to show its passage through the* small intestine and to determine whether the disease has affected the terminal ileum In the experience of the writers this is unusual and the passage through the *small intestine is generally normal in all respects On the other hand the passage* of the meal through the colon is so rapid that little can be learnt from this method Using the opaque enema the fluid tends to fill the colon with great rapidity and



FIG 213 —Barium enema ulcerative colitis showing *pseudopolyposis*

may even flood the coils of terminal ileum obscuring in doing so details of the pelvic colon It is advisable therefore to take skiagrams at frequent *intervals* The earliest changes demonstrable by radiological examination are a smoothness of outline and the loss of the mucosal haustra (Hawkins and Hardy 1950) This is first seen in the pelvic colon *but later involves the entire large bowel (Fig 209)* As the disease extends the rectum becomes narrower and the normal ampulla

such as Casilan or Prosol added to a pint of milk and suitably flavoured will supply about 60 grams of protein Bemax and soya bean flour are also useful The salt intake must be supervised and kept up and potassium supplied in the form of pureed vegetables For further details the reader should refer to the article in *Medical Treatment* edited by Geoffrey Evans (1951)

Sulphonamides and antibiotics

The insoluble sulphonamides succinylsulphathiazole and phthalysulphathiazole and the more recent antibiotics such as chloramphenicol and aureomycin have a place in treatment though results vary and are determined only by trial and error The place of the insoluble sulphonamides succinylsulphathiazole and phthalylsulphathiazole has not been definitely established but the writers believe that they have a place particularly in controlling secondary infections before surgery Full doses 10–20 grams daily are requisite and should be given over a period of 1–2 weeks at least or for a period of 3–4 days prior to ileostomy An occasional blood level should be determined for though in the great majority of cases absorption is negligible it has been the experience of the Birmingham School that where the small intestine is involved sulphathiazole may be split off before the colon is reached and absorption occur In one such case the use of succinyl sulphathiazole after ileostomy produced a blood level of 38 millilitres per 100 cubic centimetres and in spite of treatment the patient died from acute renal failure It seems probably that in these cases and in cases of steatorrhoea where succinyl sulphathiazole and phthalylsulphathiazole may also be absorbed some alteration occurs in the flora of the small intestine whereby sulphathiazole is split off

The authors experience with antibiotic therapy extends to a trial in 25 cases 10 treated with streptomycin 10 with aureomycin and 5 with chloramphenicol Streptomycin rapidly sterilizes the bowel but after 4 days the organisms have developed a high degree of resistance and its use therefore should be limited to those occasions when a rapid temporary effect is desired such as the preparation for colectomy after an earlier ileostomy Chloramphenicol and aureomycin are certainly effective in many cases of ulcerative colitis and of the two aureomycin when available with its wider range of activity is the drug of choice (D aring and Heilman 1950) Some improvement is usually obtainable and it may very occa sionally amount to a complete remission The patient feels better the temperature drops the stools lessen and become more formed and the proctoscopic appearances improve to a degree rarely seen in comparable time with ordinary medical treat ment The effective dose so far as is known is from 3 to 4 grams daily in doses of 0 75 gram The only side effects of importance are nausea and vomiting which may be troublesome but can usually be controlled either by an antacid such as Aludrox or by breaking up the dosage into smaller quantities given more frequently It must be added regretfully that the antibiotics so far introduced and so far observed have no curative effect on the established disease

Cortisone and ACTH

Reports on the use of these substances are conflicting and it is too early to offer any reliable guide as to their place in treatment Encouraging results were obtained by Gray and others (1951) who obtained satisfactory remissions in 5 of 6 severely ill patients completely incapacitated by their disease and refractory to any

follow up with periodical barium and sigmoidoscopic studies and reinforcing strongly the case for removing the entire colon after an ileostomy The source of the malignant degeneration is unknown but it does not appear that the pseudopolyps play any special part in its development

Skin and joints—Of the systemic complications, skin lesions and arthritis are the most common and are not infrequently associated (Rice Oxley and Truelove 1950) These authors quote *erythema nodosum erythematous rashes pustular* rashes purpura ulceration of the legs and urticaria as occurring in their series Pyoderma gangrenosum a grave but happily rare complication has also been described (Ricketts and others *1948*) This consists of an extensive confluent pustular eruption with marked tendency to spread The infection is not a specific one indeed the pus may be sterile It is very resistant to treatment and removal of the colon may ultimately be necessary

Arthritis occurs in some 5–10 per cent of patients It appears as a rapid swelling of a joint or joints and usually involves the knees and ankles less *commonly* the shoulders elbows and wrists It varies with the progress of the disease disappearing with a remission reappearing with a relapse Total colectomy *may ultimately be necessary to prevent permanent joint changes In two of the* writers cases the arthritis persisted after ileostomy but disappeared in one case after colectomy in the other only after ultimate removal of the rectum

Fatty liver—Recent studies have brought evidence that the liver is liable to damage during the course of ulcerative colitis Fatty changes are not uncommon (Pollard and Block 1948 Jones and others 1950) but cirrhosis is rare (Tumen and others 1947) Clinical evidence of hepatic disease is quite exceptional and the usual tests of function give equivocal results which are not in the writers *experience commensurate with either the duration or the severity of the colitis* It has been suggested that nutritional factors may be in part responsible and there is certainly a heavy drain of protein from the body in the faecal discharges Nevertheless *hypoproteinaemia has not been a feature in the writers experience* and in their last 25 cases the serum albumin has been below 3 grams in 4 cases only and the total protein below 6 grams in a like number oedema was present in 2 cases only The conclusions that may be drawn are two the intake of protein must be kept high 120 grams daily or thereabouts and an attempt to assess hepatic function should precede surgical treatment

TREATMENT

In the absence of any specific therapy fundamental principles assume great importance These are prolonged rest with suitable occupational therapy a generous diet high in proteins vitamins *and calories and low in residue abundant fluids* and adequate mineral salts especially sodium and potassium and the use of iron and blood transfusions

The great importance of the diet and particularly its protein *content has* already been emphasized by reference to the fatty changes occurring in the liver and the possibility of their nutritional origin A daily intake of 120 grams of protein should be aimed at This may be attained more easily by the use of fortified milk thus two ounces of skim milk powder and one ounce of a high protein food

the sigmoid colon and rectum bear the brunt of the disease from which they seldom recover

Despite the natural disinclination to embark on a course of treatment necessitating at the outset an artificial anus which will almost certainly be permanent and usually involving the removal of the large bowel it has become clear that in many cases these are inevitable and indeed patients frequently welcome this course rather than continue with diarrhoea which is not only incapacitating but undermines morale The mortality rate of the disease when treated conservatively is high and as has been stated is especially so in the year of onset Cures are very few and some degree of invalidism the fate of at least half the patients It is too early yet to assess the value of ileostomy as a means of lowering the death rate but there is no question at all that in many cases it completely transforms the patient s outlook With the aid of a bag of Koenig Rutzen type to control the discharges it can turn the invalid into an active member of society (Fig 214)

The main indications for ileostomy are cases of recent onset which have failed to respond to thorough medical treatment within say 6 months next come the relapsing types of cases and lastly fulminating cases In these the mortality is very high Nevertheless with modern antibiotic therapy and improvements in surgical technique and anaesthesia the risk is a decreasing one and they should probably be given the opportunity of surgery

The approach to the question of ileostomy must be gradual The operation must always be carefully planned and forethought taken to bring the patient to it in the best possible mental and physical condition After a full course of medical treatment ileostomy is considered if the colitis is still active as shown by constitutional symptoms sigmoidoscopy radiology examination of the faeces and so on The subject is cautiously broached on a ward round or by an experienced Sister to the patient and her relations In a ward where there may be other cases of ulcerative colitis in various stages of illness the subj ct will doubtless be discussed among the patients themselves It is excellent practice to encourage those patients who have had successful ileostomy to re visit the wards and help tho e who have yet to make up their minds

Briefly an attempt is made to bring the patient to ileostomy and not ileostomy to the patient The operation is not undertaken until the patient and her relations know and accept exactly what is contemplated and fully realize that thi is likely to be permanent Further the patient should at the same time be informed that a second operation for removal of the diseased colon will in all probability be advisable

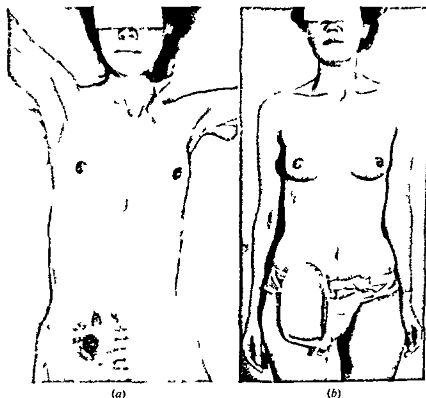
Ileostomy

The operation of ileostomy is best performed in a period of quiescence or relative remission and this can usually be induced by medical care It is most hazardous when done as a measure of last resort in fulminating cases but can be successfully achieved after suitable pre operative care even in those cases whose condition slowly but steadily deteriorates despite full medical treatment provided that the decision to operate is not too long delayed Two factors control the type of operation to be performed the form of the bag to be fitted to the ileal stump

other form of medical management The optimum period of therapy appeared to lie between 3–6 weeks with daily doses of 80–160 milligrams of ACTH depending on individual requirements Dosage did not appear to be related to the age or weight of the patient nor to the severity of the disease A sense of well being increase in appetite fall in temperature and an improvement in the stools were noted after about 4 days therapy but changes in the sigmoidoscopic picture did not appear until after 3 weeks of treatment when the mucosa became less friable and bleeding and granularity were notably lessened In no instance however did the mucous membrane revert to normal The authors believe that ACTH may prove exceedingly helpful in improving the risk of seriously ill patients who require ileostomy a view which has also been advanced by Lahey (1951) in a recent review of surgical treatment

Surgical treatment

In the treatment of ulcerative colitis apart from its complications surgery aims first at diversion of the faecal stream by ileostomy and later if symptoms or



(a) (b)

FIG 214 This woman aged 33 years weighed 4 stone at (a) the time of ileostomy and (b) seven months later 7 stone and was fully active

complications persist the removal of the large bowel Appendicostomy and caecostomy are ineffective and colostomy in a healthy area of colon rarely feasible Likewise ileo-sigmoidostomy is impracticable for in the great majority of cases

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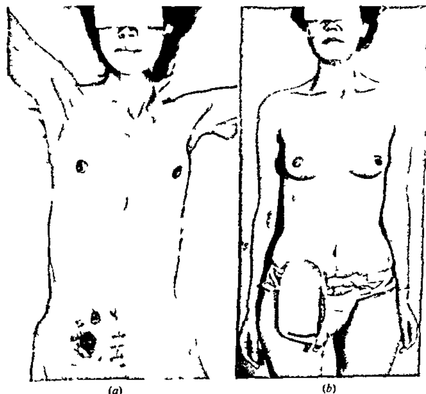
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muscle cutting incision with the ileal limbs placed at either end (Hardy and others 1949) As an alternative the method suggested by Lahey (1951) of making a paramedian incision to accommodate the distal end and a stab incision laterally for the proximal stoma facilitates examination of the abdominal contents so far as this is desirable and also provides undamaged skin around the functioning stoma Since the flange of the bag must not impinge on the anterior superior iliac spine or upon the stoma of the distal end the exact position of the incision is important and allowance must b made for the proximal end to have at least 2 inches clearance The distal end is placed higher in order to avoid the bag which is hanging from the proximal stoma but the waistline should b avoided especially in women From this point on the technique is designed to obviate certain post operative complications but as an important generalization it should be said that the performance of the operation should be done in a deliberate and unhurried manner however desperate the condition of the patient there is no place for undue haste and indeed this invites trouble later

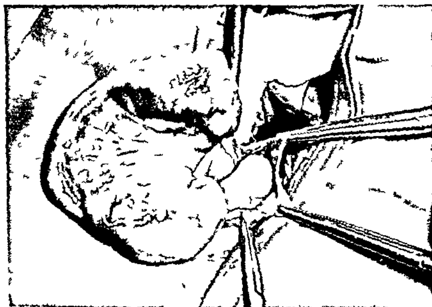


FIG 216—A fold of peritoneum held up by clamps below the caecum is included in a purse-string suture in order to close the paraileal gutter

As regards anaesthesia it is better that anxious and overwrought patients should be asleep so that general anaesthesia is preferable to local or spinal pentothal nitrous oxide and oxygen will often suffice to give adequate relaxation in these wasted patients though curare and cyclopropane may be necessary in addition If post anaesthetic vomiting can be avoided by withholding volatile anaesthetics the problem of salt depletion is reduced

and the subsequent medical treatment The Koenig Rutzen bag and its modifications (Fig 215) have proved satisfactory they are designed to be adapted to a single stump so that a terminal or separated end ileostomy is required If the proximal end is brought out alone and the distal end closed and dropped back into the abdomen treatment of the diseased colon at a later date by lavage is rendered impossible and furthermore there is a danger that stricture formation in the colon will cause a closed loop with its attendant dangers The separated end ileostomy is therefore the operation of choice

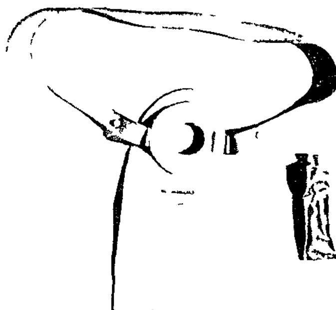


Fig 215 —Salt s modification of the Koenig Rutzen bag

Next to the psychological preparation of the patient the avoidance of certain post operative complications provides the major consideration in the pre operative treatment The hazards of ileostomy have hitherto lain in rapidly occurring peripheral vascular failure as a result of salt depletion in infection and in mechanical difficulties and failures of technique The dietary salt is increased by an additional 3–6 grams daily before ileostomy in order to build up tolerance and immediately before operation physiological saline is sometimes given intravenously Succinyl sulphathiazole or phthalylsulphathiazole renders the ileal contents either sterile or bacterially innocuous and should as already mentioned be given for 3 days prior to operation to guard against wound infection Antibiotics are to be avoided their use at this stage and post operatively may encourage the development of resistant organisms and they should be held in reserve for the subsequent treatment of the colon and for any possible complications

Technique —An incision of the McBurney type gives adequate exposure for the operation a stab incision at a higher level being added to accommodate the distal end Should it prove inadequate it may be converted into a Rutherford Morrison

milk fortified in the way already suggested Later when ileal function is stabilized a full normal diet with adequate roughage suits most patients Cereals salads and most green vegetables produce a good stiff stool and this quality can be enhanced if necessary by the addition of one of the preparations of psyllium seeds such as I so gel All that has to be learnt are the foods which tend to produce overaction of the terminal ileum they are few show much individual variation and must be found by trial and error Fried foods spicy foods and fruit juices are especially likely to make the stools loose Spinach also has this tendency as have rhubarb and treacle In some fruits notably oranges the pulp can be eaten with impunity when the juice cannot but the personal equation is such that only very general rules for guidance can be laid down (Hardy and others 1949)

Post operative complications—One complication namely subacute intestinal obstruction does arise and cause some anxiety It occurs from about the fourth day onwards and may be delayed as much as 3–4 weeks The symptoms consist of distension and colic sometimes with vomiting Wind is usually passed save in the exceptional case which requires operation for the division of adhesions The majority of cases clear up in the course of a few days and are apparently due to temporary kinks and angulations consequent upon the fixation of a normally mobile intestine The retrograde passage of a rubber catheter into the proximal stoma may be attempted in an endeavour to reduce the kinks in the lower ileum but this manoeuvre frequently fails in which case a small enema of normal saline may be effective Stenosis of the proximal stump is a further cause of partial obstruction which may give rise to colic before the passage of a motion The mucous membrane at the stump evaginates during the first 2 post operative weeks and the cut edge becomes adherent to the serosal layer at skin level a contracture of this edge due to scar tissue may then produce stenosis from 3–6 weeks after operation This may be avoided by manual eversion of the mucosa at the time of operation and by suturing it directly to the skin and it can be corrected by digital dilatation or failing that excision of the scar around the vent and resuture after a V shaped wedge has been removed from the external mucosal layer

Peritonitis has proved to be only a theoretical possibility but infection has been manifest once as cellulitis of the abdominal wall since the pre operative use of the insoluble sulphonamides following thi case there has been no further trouble of this kind The discharges from the ileum frequently excoriate the skin of the abdominal wall though the immediate application of the bag does much to minimize this The ulceration develops at any time after a week and may prove obstinate to treatment sometimes the soreness necessitates the discarding of the bag for a period while the skin is protected with Baltimore paste or a bland ointment Its persistence should not give rise to concern for it always heals and once healed s ldom recurs Herniation has never developed around the stumps likewise stump recession and prolapse have also been avoided it is felt that these complications should not arise if careful attention has been paid to the technique of operation Finally it should be appreciated that with modern technique and clo e co operation between physician and surgeon the operative mortality should be low In 27 cases there has been one death (Brooke 1951) which compares with

On opening the abdomen the appendix is removed for not only does this organ usually show signs of inflammation often with stenosis but its removal at a later date would call for appendicectomy under the difficult circumstances of a neighbouring ileostomy Despite the disorganization of the caecum resulting from the colitis this procedure has never given rise to trouble Though manipulation inside the abdomen should be reduced to a minimum it is advantageous to examine the lower 2 feet of ileum for a Meckel s diverticulum may be present and the ileostomy can then be performed at this level with re section of the portion of bowel con taining the diverticulum this examination also ensures that the lower ileum is not involved in the disease Otherwise it is usual to select a point 6–10 inches above the ileo colic sphincter for the level of section here the mesentery is divided and the vessels ligated with due regard to the conformity of the arcades and after division of the bowel the distal end is withdrawn through a stab incision At this stage two most important manoeuvres must be executed first the cut edge of mesentery which is now straightened out in linear fashion is sutured throughout its length to the peritoneum of the anterior abdominal wall and secondly a purse string suture at right angles to this is passed from the mesentery below the caecum and out through the peritoneum on the lateral side of the wound to obliterate the paraileal gutter (Fig 216) Two purposes are thus served Obstruction is avoided by preventing a loop of bowel passing either between the natural V of the cut mesen teric edge and the anterior abdominal wall or around the ileostomy in the gutter lateral to it Prolapse of the proximal loop a common sequel to ileostomy is also prevented since the mesentery is thus securely fixed and the bowel wall proximal to the stoma anchored Finally the abdominal wounds are sutured around the ileal ends so that about one inch of bowel protrudes No attempt is made to seal the proximal end by tying in a rubber tube since the valvulae conniventes tend to prevent its passage for any distance even under guidance from a hand manipulating it from outside the bowel before the abdomen is closed The Koenig Rutzen bag may be placed in position before the patient leaves the theatre or on arrival in the ward The whole operation takes from 1 to 1½ hours to perform

Post operative care —Care must be taken in the immediate post operative period to maintain an adequate salt intake a reading of 4–6 grams per litre of urine (Fantus 1936) being satisfactory An addition to the dietary salt is usually sufficient to obviate the sudden crises of peripheral vascular failure from salt depletion but in severely ill and dehydrated patients the intravenous route for 48–72 hours after operation gives a more delicate and rapid control Over dosage may be anticipated by a study of the fluid chart As the ileum settles down to normal function the danger passes but patients should be advised to be liberal with their salt at all times

The action of the stoma varies within wide limits the chief factors being the diet emotional stimuli and the previous physiological pattern Generally speaking the stoma acts during and for a short time after the main meals and in most patients freely during the night With the new bag patients are often oblivious of the discharge and sleep is undisturbed

The risks of post operative obstruction demand caution in feeding for the first 2 or 3 weeks During this period a high-calorie high protein and low residue diet in concentrated fluid form is probably best additional protein being supplied by

endeavour should be made to preserve the omentum though gross inflammation and adherence to the colon may render this impracticable When the ileal end is reached the mesentery is detached close to the bowel to avoid damage to the blood supply of the proximal stump This free edge should later be attached laterally in order to strengthen the closure of the paraileal gutt r and to prevent prolapse in the remaining stump for this has occurred once as a result of the detachment of the mesentery An elliptical incision around the distal stoma frees the last part of the bowel No attempt need be made to cover the raw surfaces with peritoneum and this view is amply supported by the work of Strauss (1944) of Bacon and Trimpi (1950) and of Robins and others (1949) Indeed to do so invites com plications for a dead space is then produced which may become infected if not drained and the small bowel snared and obstructed where the p ritoneal suture line must necessarily cease at hepatic and splenic levels Apart from one death on the fourth post operative day from renal failure in a patient with gross degeneration of liver and kidneys these are the only complications which have been encountered in 12 cases of total colectomy and no trouble has occurred since peritonealization has been abandoned In marked contrast to the convalescence following ileostomy the post operative course is usually straightforward and no more care is required than is usually given to a patient who has had a laparotomy As after ileostomy chemotherapy and antibiotics are held in reserve for possible complications

Perineal excision

Removal of the colon may suffice but should the disease persist in the rectum or the anal canal or rectal complications already mentioned be present then this organ must be removed by the perineal route after a suitable period of convales cence The operation differs from perineal excision for other causes only in being technically more difficult for the perirectal tissues are inflamed and planes of cleavage may be hard to find as the upper end of the rectum is approached the ureters will often be found to be closely adherent

General conclusions on surgical treatment

Sufficient time not less than one year has now elapsed to permit a tentative assessment of some 20 cases 10 following ileostomy alone and 10 after colectomy or colectomy and excision of the rectum Of the patients who have had ileostomy alone 9 have returned to full work with an average gain in weight of over 3 stone The 10 patients needing further operation had already increased their weight from 1 to 2 stone after ileostomy and the subsequent operations have added to this and substantially improved their general health

It may be concluded therefore that surgical treatment has much to offer selected patients suffering from ulcerative colitis In spite of the anxieties and dis comforts inseparable from a protracted routine and a convalescence fraught with difficulties in particular after ileostomy surgery is abundantly justified by its results After operation nutrition improves rapidly and weight is regained some times at a remarkable speed Even more encouraging is the improvement in the patient s general outlook and when the technique of the bag has been mastered normal life can be resumed including a full day s work and a return to such recreations as swimming tennis and dancing

the mortality of 4 per cent in Strauss (1944) series of 104 ileostomies This fatality was due to the technical failure of omitting to close the paraileal gutter so that obstruction ensued

Colectomy

Removal of the large intestine is the logical sequel to ileostomy In a few cases the colon becomes quiescent after ileostomy and health is unimpaired in a few more infection can be controlled by periodic lavage through the distal stoma with streptomycin and penicillin as mentioned later In the majority however infection continues with frequent rectal discharges of pus mucus and blood which do much to nullify the initial benefits of ileostomy As has already been mentioned there are certain complications such as rectal strictures recto vaginal fistulae and other intractable ano rectal lesions which may demand colectomy for satisfactory healing Persistent or recurring arthritis occasionally comes into this category if permanent joint damage is to be avoided and again the case for total colectomy is strongly reinforced by the increased liability of these cases to develop malignant disease

Led by the example of Lahey (1941) and Cattell (1944 1948) it has been the practice of most surgeons to remove the colon in stages It is true that in 1924 Strauss performed total colectomy in one stage but later (1944) gave this up More recently however Dennis (1945) has broken away from piecemeal colectomies and Miller (1949) has even performed primary colectomy without previous ileostomy in selected cases There can be no doubt that the improvement wrought in recent years in anaesthetics in the methods of infusion and transfusion together with the advent of chemotherapy and antibiotics has enabled the patient who has benefited from ileostomy to withstand well total colectomy in one stage indeed such a procedure is probably safer for it reduces the risks of multiple operations and removes the site of the disease almost *in toto* leaving only the minimal area of the rectum Colectomy does not follow ileostomy immediately a period of from 6 weeks to 6 months may be required for the patient to obtain that benefit of gain in weight and strength that usually accrues from the initial operation

Remarkably few descriptions of the technique of total colectomy in one stage have been given and in none have the special difficulties consequent upon the presence of the ileostomy been taken into account For 4 days prior to the operation infection in the colon is reduced by irrigating a pint of normal saline containing 1 gram of streptomycin and 1 mega unit of penicillin through the distal ileal limb in 24 hours The patient proceeds to the theatre with the Koenig Rutzen bag in place this is cleansed together with the skin and covered with a skin towel A left paramedian incision starting from within one inch of the pubes and extending to the lower epigastrium gives adequate exposure The resection is then started at the distal end and the operation proceeds in retrograde fashion for in this way the removal of the distal ileal limb is made easier than when the operation is conducted from above downwards The bowel is divided at the top of the rectum the end of which is closed and placed below peritoneal level By doing this the final operation is limited to a perineal resection and the abdomen need not be opened if the rectum has to be removed later division of the superior haemorrhoidal vessels at the time the bowel is cut across facilitates subsequent removal of the rectum and causes no harm As the operation proceeds to the transverse colon an

endeavour should be made to preserve the omentum though gross inflammation and adherence to the colon may render this impracticable When the ileal end is reached the mesentery is detached close to the bowel to avoid damage to the blood supply of the proximal stump This free edge should later be attached laterally in order to strengthen the closure of the paraileal gutter and to prevent prolapse in the remaining stump for this has occurred once as a result of the detachment of the mesentery An elliptical incision around the distal stoma frees the last part of the bowel No attempt need be made to cover the raw surfaces with peritoneum and this view is amply supported by the work of Strauss (1944) of Bacon and Trimpi (1950) and of Robins and others (1949) Indeed to do so invites complications for a dead space is then produced which may become infected if not drained and the small bowel snared and obstructed where the peritoneal suture line must necessarily cease at hepatic and splenic levels Apart from one death on the fourth post operative day from renal failure in a patient with gross degeneration of liver and kidneys these are the only complications which have been encountered in 12 cases of total colectomy and no trouble has occurred since peritonealization has been abandoned In marked contrast to the convalescence following ileostomy the post operative course is usually straightforward and no more care is required than is usually given to a patient who has had a laparotomy As after ileostomy chemotherapy and antibiotics are held in reserve for possible complications

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REFERENCES

Bacon H E and Trimpi H D (1950) *Surg Gynec Obstet* **91** 409
Bockus H L (1944) *Gastroenterology* Vol II Philadelphia Saunders
Brooke B N (1951) *Ann Roy Coll Surg* **8** 440
Cattell R B (1944) *Surg Clin N Amer* **24** 661
— (1948) *Gastroenterology* **10** 63
Dearing W H and Heilman F R (1950) *Ibid* **16** 12
Dennis C (1945) *Surgery* **18** 435
Evans G (1951) *Medical Treatment* London Butterworth
Fantus J B (1936) *J Amer med Ass* **107** 14
Felsen J and Wolarsky W (1948) *Amer J Obstet Gynec* **56** 751
Fleming A and Allison V D (1922) *Brit J Exp Path* **3** 252
Glass G B Pugh B L Grace W J and Wolf S (1950) *J clin Invest* **29** 12
Grace W J Wolf S and Wolff H G (1950) *J Amer med Ass* **142** 1044
Gray S J Reifenstein R W Benson J A and Young J C G (1951) *Arch intern Med* **87** 646
Groen J (1947) *Psychosom Med* **9** 151
Hardy T L (1945) *Lancet* **1** 519
— Brooke B N and Hawkins C F (1949) *Ibid* **2** 5
Hawkins C F and Hardy T L (1950) *J Fac Radiol Lond* **11** 95
Hurst A F (1921) *Guy s Hosp Rep* **71** 26
Jackman R J Bargen J A and Helmholz H F (1940) *Amer J Dis Child* **59** 459
Jones G W Baggenstoss J and Bargen J A (1950) *Proc Mayo Clin* **25** 251
Lahey F H (1941) *N Y St J Med* **41** 475
Lium R and Porter J E (1939) *Arch intern Med* **63** 201
Miller G G Gardner C Mc and Ripstein C B (1949) *Canad med Ass J* **60** 584
Paulley J W (1950) *Gastroenterology* **16** 566
Pollard H M and Block M (1948) *Arch intern Med* **82** 159
Rice Oxley J M and Truelove S (1950) *Lancet* **1** 607 663
Ricketts W E Kirsner J B and Rothman S (1948) *Amer J Med* **5** 69
Robins G F Brunschwig A and Foote F W (1949) *Ann Surg* **130** 456
Sammons H G (1951) *Lancet* **2** 239
Sloan W P Bargen J A and Gage R P (1950) *Gastroenterology* **16** 25
Stewart G T (1950) *Brit med J* **1** 405
Strauss A Friedman J and Bloch L (1924) *Surg Clin N Am r* **4** 667
— and Strauss S (1944) *Ibid* **24** 211
Tumen H J Monaghan J F and Jobb E (1947) *Ann intern Med* **26** 542
— and Cohn E M (1950) *Gastroenterology* **16** 1
Wener J Hoff H E and Simon M A (1949) *Ibid* **12** 637
Wilks S and Moxon W (1875) *Lectures on Pathological Anatomy* 2nd ed London Churchill
Wittkower E (1938) *Brit med J* **11** 1356
Wolf S and Wolff H G (1943) *Human Gastric Function* New York Oxford University Press
Wright R D and Florey H W (1938) *Quart J exp Phys* **28** 207

CHAPTER 24

BACILLARY DYSENTERY

RODERICK ANDREW

BACILLARY dysentery results from infection of the large bowel by species of the genus *Shigella* causing diarrhoea usually with blood and mucus in the stools The modern occurrence of the disease contrasted with its ravages in the past exemplifies its main epidemiological features for it is mainly a disease of primitive societies and regression to their sanitary habits such as occurs inevitably in war leads to large epidemics Among native races particularly in the tropics the disease is still endemic and at times causes a high mortality especially in children In temperate zones the threat still lingers as shown by occasional epidemics in children s hospitals day nurseries kindergartens asylums and holiday camps Many factors provide protection—clean personal habits efficient sewerage legislation controlling the making and selling of foodstuffs pure water and milk supplies and fly control

EPIDEMIOLOGY

The source of infection is faeces from a person with dysentery Food contaminated by flies or fingers infected milk or water and rarely direct manual contact are the vehicles for spread

Carriers are the main source of epidemics Hardy and Watt (1944) in Texas cultured 6 984 specimens from faeces and found 380 grew *Shigella* At the time of examination only 36 had diarrhoea—1 overt infection for every 10 5 carriers

A considerable reduction in the number who become carriers after an attack of dysentery has been achieved by the use of the sulphonamides Before their use about 3 per cent became carriers since then rates of about 1 per cent are usual (Fortune and Ferris 1945)

The sick carrier is probably the most dangerous He is well enough to live in his normal environment and yet has diarrhoea Some have attacks so mild that they never come under medical observation It has b en clearly shown that most carriers have lesions in the rectal mucosa which can be recognized by sigmoidoscopy (Fairley and Boyd 1943) However that this is not always so was demonstrated by Thomson Parr and Donald (1943) who showed during an epidemic in troops that some may not show at any time a sign or symptom of infection may be beyond suspicion when examined by sigmoidoscopy and yet may be carriers of *Sh dysenteriae* (*Shiga*) *Sh flexneri* *Sh sonnei* or *Sh boydii*

In countries where sanitary conditions are good and temperate climates

prevail there is no definite seasonal incidence but in countries with low living standards epidemics are more common in the warmer months influenced largely by fly dissemination

PATHOLOGY

In spite of the huge incidence of bacillary dysentery in World War II little was added to what had been established by Manson Bahr 1943 Rogers 1921 Dew and Fairley 1921

Pathological changes in all but a few severe or fatal cases are confined to the large bowel and the brunt being borne in the rectum it is easy to observe the living pathology through the sigmoidoscope

In the acute phase the earliest changes are hyperaemia and excess mucus formation Within a day or two small submucosal haemorrhages and ulcers appear against a background of universally inflamed and thickened mucosa which is intensely engorged and friable The ulcers are superficially irregular in outline and a few millimetres in diameter In fulminating cases coagulation necrosis may occur stripping the whole mucosa and leaving a haemorrhagic granular surface

Subacute cases are occasionally seen in which discrete papule like lesions due to abscess formation in the lymphoid follicles are found and these break down to small ulcers (Manson Bahr 1943 Andrew 1946) Lesions of this nature are the probable source of organisms in most carriers

BACTERIOLOGY

No universally accepted classification can be given for the genus *Shigella* That proposed by Ewing (1949) based largely on the work of Boyd (1948) appears to be the best so far proposed

TABLE I

THE GENUS SHIGELLA

Ewing s designation		Previous designations
GROUP A		
Shigella dysenteriae	I	Shiga
	II	Schmitz Ambigua
	III	Q771 of Large Sachs group
	IV	Q1167 of Large Sachs group
	V	Q1030 of Large Sachs group
	VI	Q454 of Large Sachs group
	VII	Q902 of Large Sachs group
GROUP B		
Shigella flexneri	I	*Flexner V and Flexner VZ*
	II	Flexner W Flexner WX Flexner X Flexner Y
	III	Flexner Z
	IV	Boyd 103
	V	Boyd P 119
	VI	Boyd 88 Newcastle and Manchester bacilli

TABLE I—*continued*

THE GENUS SHIGELLA—*continued*

Ewing's designation		Previous designations
GROUP C		
Shigella boydii	I	Boyd I Boyd 170
	II	Boyd II Boyd P.288
	III	Boyd III Boyd D 1
	IV	Boyd IV Boyd P 274
	V	Boyd V Boyd P 143
	VI	Boyd VI Boyd D 19
	VII	*Shigella etousae*
GROUP D		
Shigella sonnei		B Sonne Duval
Shigella dispar	I	
	II	
GROUP E		
Shigella alkalescens		

Group A includes the non fermenters of mannite and lactose Groups B and C are made up of mannite fermenters lactose non fermenters and those in Group D are slow lactose fermenters The subdivisions are made by serological methods using the organism isolated and type specific anti sera

CLINICAL ASPECTS

The incubation period is usually 2–3 days but may be as long as a week and has been recorded as short as 10 hours in an experimental infection (Andrew 1946)

In most the onset is sudden with diarrhoea and lower abdominal colicky pain Many vomit but tenesmus in an infection of average severity is not common (Hone Keogh and Andrew 1942) Blood and mucus are frequently found in the stools within a day of onset and up to 30–40 motions may be passed in 24 hours in severe cases Some attacks are extremely mild 2–3 loose motions and vague abdominal discomfort lasting a day or two constituting the attack Many cases of Gyppy Tummy of this nature in the Middle East are due to dysentery organisms

Fulminating infections show marked toxaemia fever is high incontinence of faeces occurs and dehydration is severe Delirium or coma may supervene Recovery may occur even in such desperately ill patients treated with *Sulphaguanidine*

Patients with an infection of average severity begin to show improvement within a few days and after a week the diarrhoea has ceased whether treated with sulpha drugs or symptomatically The course of severe cases is undoubtedly cut short by sulphonamides

Considerable variations in the clinical picture are to be expected in epidemics —high fever and abdominal pain for a day or so before diarrhoea proves the obvious clue to the diagnosis abdominal symptoms closely simulating acute

appendicitis meningitic symptoms predominating and symptoms suggesting pneumonia

Chronic bacillary dysentery is rare It was considered to be relatively common after World War I and yet during and subsequent to World War II very few cases of acute bacillary dysentery developed a chronic dysentery Only one case of chronic bacillary dysentery was seen by the author in about 1 000 cases observed in the Middle East 1940–42 and none was seen in New Guinea nor have any been discovered at a large Repatriation Hospital for ex service men The universal use of sulphonamides from 1941 onwards may well have a bearing on this discrepancy of experiences by medical officers in the two World Wars The clinical and pathological features are indistinguishable from ulcerative colitis and it is possible that many patients thought to have chronic bacillary dysentery had in fact ulcerative colitis which grants no immunity from dysentery infection

A series of cases called post dysenteric colitis has been described by Stewart (1950) These followed infection by dysentery bacilli or amoebae He divided them into three groups—non ulcerative ulcerative due to non specific bacterial infection and ulcerative akin to idiopathic ulcerative colitis Where no organic lesion can be demonstrated the syndrome he describes is not different from the common disorder of peace and war variously called the irritable colon unstable colon spastic colon or mucous colitis

Felsen (1945) considers ulcerative colitis and chronic distal ileitis (Crohn s disease) to be the end result of bacillary dysentery Direct evidence for his view is lacking Were this true one would expect a notable increase in the incidence of these diseases in ex service men This has not occurred

Complications of bacillary dysentery are uncommon A large number has been described by Fairley and Boyd (1943) from collected series and these include haemorrhage perforation portal pyaemia toxic arthritis peripheral neuritis and renal failure

The mortality in well nourished healthy adults is low In the Australian Military Forces only 19 deaths occurred (1939–46) out of 21 015 reported cases Many thousands of unreported cases occurred in this period Even before sulphonamides were introduced towards the end of 1941 the death rate was very small although occasional fulminating and fatal cases demonstrated the potential virulence of the organisms In children the aged and in native races high death rates have been observed (Felsen 1945)

DIAGNOSIS

While bacillary dysentery usually occurs in epidemic form and can readily be recognized by the symptoms already described a proportion will be diagnosed only by exact bacteriological methods From some cases no organisms are isolated and the diagnosis depends on the clinical features cytodiagnosis and sigmoidoscopy The carrier state can be proved only by the isolation of *Shigella* organisms and the types responsible need to be known for adequate epidemiological knowledge and control The disease lends itself to exact bacteriological identification in most cases and for this it is essential to use a stool recently passed Fresh specimens will yield a higher percentage of isolations and the identification of *Entamoeba*

histolytica in the vegetative form is impossible without this precaution

Mucus from the stool is examined microscopically for protozoa—bacillary and amoebic dysentery occasionally coexist—and for cells Typically a bacillary exudate consisting of red blood cells pus cells and macrophages is found At the onset and in the recovery phase of most and throughout the disease in some an indefinite exudate is seen consisting of mucoid secretion with scanty pus cells and perhaps a few red blood cells

Mucus is inoculated on to the s lected culture medium For routine work MacConkey s and desoxycholate citrate agar are excellent After incubation at 37 C for 18–24 hours any non lactose fermenting colonies are subcultured on an agar slope and also inoculated into lactose glucose and mannitol solutions Exact identification can be made on the second day in many from the fermentation reaction and slide agglutination tests using type specific anti s ra and ag r slope material

Samples may conveniently be collected by rectal swabs taken by a swab stick which is passed through a rubber tube blindly inserted into the rectum (Hardy Watt and de Capito 1943) Absolutely fresh specimens can b obtained in this way and it is of great advantage in children and for mass surveys where carriers are sought

Serological tests for antibodies are quite unreliable in bacillary dysentery

DIFFERENTIAL DIAGNOSIS

It needs emphasis that skilled cytological and bacteriological methods are necessary for differentiating the various infective causes of dysentery Amoebic and other rare protozoal and flagellate dysenteries typhoid fever and salmonella infections cannot be diagnosed with any certainty in their initial phases on clinical grounds alone and all may be remarkably similar at the bedside Sigmoidoscopy is of great importance as it will reveal whether one of the group which cause colitis is present and exclude the salmonella typhoid group where only the small bowel is involved Ulcerative colitis may closely mimic dysentery and repeated failure to culture *Shigella* organisms or find amoebae with a poor or absent response to specific therapy usually first arouses suspicion

MANAGEMENT

Ward management

Ward management includes the proper isolation of patients in fly proof wards with adequate cupboard space for bed pans (Hone and others 1942) Each patient should be instructed to pass a morning stool in a bed pan for the physician s inspection The indications of progress are to be found by examination of the patient and his excreta Nurses and orderlies should be trained in the methods of specimen collecting for the laboratory and assistance at sigmoidoscopic examinations

Nursing

In the first few days bed rest is usually necessary although many mild cases can be allowed bathroom privileges throughout Patients with severe infections may be incontinent and cotton wool should be packed under the buttocks and changed frequently Most patients are fully ambulatory by the end of the first week

Diet

Dietetic restrictions need seldom be severe or irksome Fluids in generous amounts should be supplied and food according to the patient s appetite Milk may be given throughout the illness and tea and fruit juices as required Appetite is poor for the first few days and a bland diet of low residue consisting mainly of eggs and carbohydrates is adequate With the return of appetite white meat fish and puree vegetables may be added Food with a high roughage content should be avoided for several weeks

Drugs

Purging is not required at any stage of the illness Opium and its derivatives may be used freely for pain Fluids may need to be given intravenously in fulminating infections and for these patients 5 per cent glucose in water 5 per cent glucose in normal saline serum or protein hydrolysates with the usual indications may be required Hypokalaemia has been noticed by the author in severe cases of ulcerative colitis and this deficiency should be sought by serum potassium estimations and electrocardiography and corrected if found

The introduction of sulphaguanidine by Marshall and others (1940) revolutionized the treatment of bacillary dysentery Other sulphonamides of similar low solubility have been developed and some have advantages over sulphaguanidine The soluble sulpha drugs such as sulphamerazine and sulphadiazine have been used also with success However the proven safety and effectiveness of sulphaguanidine used on a vast scale in World War II makes it still the drug of choice It is however largely ineffective against *Sh sonnei* and for this organism sulphadiazine should be used (Hardy 1946) This is of importance in the United Kingdom where Sonne infections are the most common type

Table II shows the dosages for three sulphonamides of low solubility and these only should be used as a rule in the tropics because the dangers of renal complications are increased when soluble sulphonamides are used in the presence of highly concentrated urine

Chloramphenicol has been shown to be effective in Sonne dysentery (Mazursky 1950 Ross and others 1950) Bacteriophage anti dysenteric sera and intestinal disinfectants are only of historical interest

TABLE II

	Initial dose	Subsequent dosage	
		Until diarrhoea controlled	Until cured
Sulphanilylguanidine (Sulphaguanidine)	7 0 g	3 0 g q i d	3 0 g t d s
Succinylsulphathiozole (Sulphasuxidine)	5 0 g	2 0 g q i d	2·0 g t d s
Phthalylsulphathiozole (Sulphathaladine)	1 5 g	1 0 g q i d	0 5 g q i d

Treatment aims at rapid and complete control of the infection Prevention of the development of a carrier state is of supreme importance and for this accurate bacteriological methods are necessary Certain criteria of cure therefore should be fulfilled (a) the patient well and passing formed motions normal macro and microscopically (b) sigmoidoscopic appearances normal and (c) stool cultures negative for *Shigella* In peace time all these should be satisfied Exigencies of war may frustrate the realization of this ideal but the closer they are followed the quicker are epidemics controlled Hygiene and sanitation of a high order are the most important factors in prevention and control but local conditions ignorance and war may cause a complete breakdown in their application Vaccines and bacteriophage have proved of no value in prevention A notable example of blanket drug control occurred in the jungles of New Guinea during World War II (Andrew 1946) It was impossible in this campaign to apply orthodox methods and a disastrous epidemic was halted by treating every case of diarrhoea in the force with sulphaguanidine from the onset of symptoms

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REFERENCES

Andrew R (1946) *Med J Aust* 2 299
Australian Military Forces Central Army Records Personal communication
Boyd J S K (1948) *J trop Med Hyg* 51 169
Dew H R and Fairley N H (1921) *Med J Aust* 1 453
Ewing W H (1949) *J Bact* 57 633
Fairley N H and Boyd J S K (1943) *Trans R Soc trop Med Hyg* 36 253
Felsen J (1945) *Bacillary Dysentery Colitis and Enteritis* Philadelphia Saunders
Fortune C and Ferris A A (1945) *Med J Aust* 1 337
Hardy A V and Watt J (1944) *J Amer med Ass* 124 1173
— Watt J and de Capito T (1943) *Pub Hlth Rep* 58 696
— (1946) *Ibid* 61 857
Hone F R Keogh E V and Andrew R (1942) *Med J Aust* 1 631
Manson Bahr P H (1943) *The Dysenteric Disorders* 2nd ed London Cassell
Marshall E K Bratton A C White H J and Litchfield J T (1940) *Bull Johns Hopk Hosp* 67 163
Mazursky M M (1950) *J Pediat* 37 238
Rogers L (1921) *Bowel Diseases in the Tropics* London Oxford University Press
Ross S Burke F G Rice F C Washington J A and Stevens S (1950) *J Amer med Ass* 143 1459
Stewart C T (1950) *Brit med J* 1 405
Thomson F F Parr L J A and Donald C D (1943) Personal communication

CHAPTER 25

AMOEBIASIS AND OTHER PARASITIC CONDITIONS OF THE ALIMENTARY TRACT

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INTESTINAL AMOEBIASIS

AMOEBIC DYSENTERY has been recognized since 1875 when it was first described by Losch who succeeded in transmitting the infection to a dog However despite continued research stimulated by the occurrence of many severe cases during the two World Wars there are still many gaps in our knowledge of this disease and of the dysentery amoeba *Entamoeba histolytica* which is unfortunately one of the most difficult of all living creatures to investigate

Aetiology

Although *E histolytica* has a world wide distribution amoebiasis is essentially a disease of the tropics and subtropics In Great Britain where overt amoebiasis rarely occurs some 10 per cent of the population are infected and the incidence of infection in other countries with all varieties of climate has been found to be comparable with this figure Throughout the world most persons infected with *E histolytica* are healthy carriers and the exact circumstances which govern the pathogenicity of this parasite are uncertain Variations in the susceptibility of the human host the mass of the infection the virulence of the particular strain of amoeba climate and the synergic action of bacteria are all possible factors any or all of which may play a part

E histolytica normally inhabits the large bowel where it is found within the lumen or in the wall The amoeba ingests solid food by means of its pseudopodia while fluid is absorbed through its surface For many years it was regarded as an obligatory tissue parasite invariably ulcerating or producing minute superficial lesions of the lining of the gut by means of a cytolytic ferment and feeding on red blood cells However animal experiments have shown that *E histolytica* may live as a commensal in the lumen of the intestine feeding on bacteria and other faecal contents and amoebae containing food vacuoles with enclosed bacteria have been recovered from human carriers and from cases of chronic amoebiasis Hoare (1950) considers that there is sufficient evidence to justify the recognition of a commensal phase in the life history of the parasite The amoeba multiplies by binary fission both in the tissues and within the bowel and in the latter situation it undergoes the phase of encystment the infection being spread by the contamination of food or drink with faecal material containing cysts Vegetative amoebae which are passed from the bowel by patients with dysenteric symptoms are short lived outside the body and if swallowed by man they are destroyed by the gastric juice Cysts are passed when the acute symptoms abate and these are hardy living for

weeks if kept moist and cool When swallowed they hatch in the bowel liberating small amoebae The healthy or convalescent carrier is therefore the usual source of infection

Carriers often pass large numbers of cysts in the stools and bad sanitation resulting in massive infection seems more important than climate in the localization of the disease in the tropics and subtropics where it is more prevalent during the rainy season soil polluted with cysts being washed into wells and springs After the rains flies increase and these can take up cysts when feeding on human faeces and pass them unaltered through the gut Again in the East human excreta are widely used for the fertilization of vegetable gardens so that enticing articles of food such as strawberries and salads may be heavily contaminated Most of the worst cases of chronic amoebic dysentery encountered during World War II dated from the fall of Burma in 1942 when many men escaping on foot developed dysentery during their long trek Appalling hardships were suffered along the refugee route where many died of starvation malaria dysentery and cholera, and there was little possibility of sanitation or of purification of water

Natural infection with *E histolytica* may also occur in certain lower mammals for instance monkeys rats and dogs In the laboratory the experimental infection of freshly weaned rats induced by feeding with cysts or by inoculating vegetative amoebae into the caecum is used in the testing of anti amoebic drugs Young kittens are used for testing the virulence of different strains of amoebae which as a rule are injected into the rectum the anus being kept sealed for 48 hours

For many years it has been suggested that there are races or strains of *E histolytica* which differ in virulence or pathogenicity and that a particularly virulent strain causes amoebic dysentery in its host It appears to be generally accepted that there is a small race recognized by its small cysts measuring 7 9μ in diameter which is non pathogenic never ingests red cells and which fails to produce lesions in experimentally infected animals Recent surveys in the United States and in Great Britain suggest that at least 50 per cent of healthy carriers may be infected with this small harmless race There is no agreement however as to the possible existence of different strains belonging to the larger race which has cysts with a mean diameter of 11 12μ Amoebae of this large race obtained from healthy carriers in temperate climates may prove pathogenic to laboratory animals but in Great Britain the number of published cases of indigenous amoebiasis has been very small Morton Neal and Sage (1951) have reported three recent cases in individuals who had never been out of England However two of these patients one of whom died were nurses who had been in contact with patients suffering from amoebiasis contracted overseas

Some parasitologists have long held the view that the bacteria associated with *E histolytica* in the bowel play an important part in determining its pathogenicity Judging from the response of cases of amoebic dysentery to treatment with antibiotics which are not directly amoebicidal it now seems probable that bacteria influence the course of amoebic infection

Pathology

When the usual state of host parasite equilibrium breaks down or does not exist ulceration occurs in the bowel usually in the large intestine the amoebae

multiplying and passing into the tissues They break through the muscularis mucosae and undermine the mucous membrane producing characteristic flask shaped ulcers These may coalesce and lead to large ulcerated areas In severe cases the muscular coat may be perforated leading to general peritonitis or local adhesions and abscesses The rectum caecum and colonic flexures are most affected and sometimes there may be tumour formation at these sites resulting from amoebic invasion of the bowel together with a super added pyogenic infection The inflammatory process spreads through the bowel wall into the pericolic and perirectal tissues the resulting mass consisting of fibrous and granulation tissue and varying degrees of ulceration The wall of the gut may be destroyed and small abscesses are usually present within the mass Typical amoebic ulcers are usually present but on the other hand no evidence of amoebiasis may be forthcoming the parasites dwelling in the depths of the granuloma Scarring and stricture formation in the rectum and colon may ensue as the result of pyogenic infection

The liver is always liable to attack by invading amoebae which may enter the blood stream through eroded vessels in the wall of the bowel and pass up through the portal vein causing hepatitis and liver abscess From the liver amoebae may pass into the sytemic circulation and reach other organs for instance the lung or the brain where they may colonize and give rise to abscesses Liver abscesses may rupture into the pleura lung pericardium or peritoneum Secondary amoebic infection may occur in the skin around the anus and around colostomies and the bladder urethra abdominal wall uterus and vagina have occasionally been involved as the result of direct spread of infection from the bowel

Symptoms

The symptoms of intestinal amoebiasis are extremely variable and practically any gastro intestinal disorder from mild dyspepsia to ulcerative colitis and malignant disease may be simulated Most cases fall into the chronic category In rare instances the disease may be so acute that large portions of mucous membrane become gangrenous and slough Dysentery which strictly speaking denotes diarrhoea with blood and mucus is a very important symptom but it is by no means invariable Alternating diarrhoea and constipation are not uncommon and sometimes even constipation may be the main complaint Extensive ulceration has at times been found on sigmoidoscopy in patients with normally formed stools and there have been fatal cases of this type Abdominal pain usually chronic and colicky is a common symptom and in chronic cases the caecum and descending colon are often palpable and tender Pain in the right lower quadrant may be the presenting symptom of amoebic typhlitis and many cases of amoebiasis have been operated upon mistakenly for appendicitis sometimes with fatal results

Amoeboma

Granulomatous masses may develop in the rectum caecum or colonic flexures as already described These may be palpable and visible in the rectum or they may present as abdominal tumours with obstructive symptoms As might be expected they have been mistaken for new growths of the bowel clinically and radiologically the differentiation is at times extremely difficult Since carcinoma and amoebiasis

may coexist malignancy is not excluded by the finding of *E histolytica* in the stools thus biopsy is always indicated in the case of rectal lesions When the mass is higher up in the bowel the therapeutic effect of emetine and antibiotics should be tried and if the lesion does not respond within a few days surgery must not be delayed Morgan (1944) removed a caecal tumour from a patient suffering from amoebic dysentery On removal it appeared to be an amoeboma but it was found on histological examination to be an adenocarcinoma Although an amoeboma may disappear in a dramatic fashion as the result of specific treatment subsequent fibrotic changes may lead to obstruction of the bowel In a personal series of 700 cases of chronic amoebic dysentery during World War II the incidence of rectal stricture was 1 per cent

Diagnosis

This rests upon the identification of *E histolytica* in the stools or in specimens taken at sigmoidoscopy or proctoscopy Active amoebae with included red blood corpuscles are passed by patients with amoebic dysentery and may be obtained directly from ulcers For all practical purposes these amoebae can be identified as *E histolytica* (Wenyon 1947) The specimens should be examined within a few minutes as outside the body active amoebae soon lose their motility and characteristic structure In less severe cases there may be smaller amoebae which do not contain red blood corpuscles The identification of these and of cysts which are passed in different stages of development by patients with mild symptoms and by healthy carriers is a matter for an experienced protozoologist there are four species of non pathogenic amoebae from which differentiation may be necessary It is estimated that a single stool examination reveals only 25 per cent of infected cases and if this is negative a series of six examinations on consecutive days is advisable In tests of cure six daily specimens of stool should be examined at least one month after the end of treatment

Sigmoidoscopy

This is a valuable diagnostic measure which often succeeds when other measures have failed (Manson Bahr 1947) The majority of cases have lesions in the rectum and sigmoid and active amoebae can be found if material obtained from these lesions is examined immediately in warm saline under a microscope Such material can easily be aspirated by means of a long capillary pipette In dysenteric cases there may be generalized hyperaemia of the mucous membrane with multiple haemorrhagic ulcers In more chronic cases there are discrete lesions separated by normal mucosa The e lesions vary considerably in size and appearance There may be small hyperaemic areas with yellowish centres or obvious ulcers which may be single or multiple Dark haemorrhagic sloughs may extend from the larger ulcers (Dyak hair ulcers) Crateriform pits are considered by Morton (1946) to be pathognomonic of quiescent amoebiasis calling for persistent search in the stools for cysts Bowel wash outs should not be given before the examination as the resultant hyperaemia may obscure small lesions Sigmoidoscopy which is best carried out in the knee-chest position must be preceded by digital examination of the rectum If this is not done palpable carcinomas may be missed for at times they may resemble amoebic lesions superficially Apart from its value in diagnosis the sigmoidoscope

valuable in the diagnosis of some cases of metastatic amoebiasis for instance in amoebic hepatitis where the diagnosis is often presumptive or based upon the patient s response to emetine It would also be useful in all types of case in the *routine assessment of cure*

Treatment

Intestinal amoebiasis is still a therapeutic problem in spite of enthusiastic claims made at times regarding various drugs Some have been introduced with preliminary reports of 100 per cent cures but included in these successful series are symptomless patients *passing cysts and in whom E histolytica may be living commensally* this may explain the failure of such drugs in patients with amoebic dysentery There is no general agreement as to the policy to be adopted concerning so called cyst passers *At present it seems rational to treat those who have symptoms and those* who may have been infected in countries where amoebic dysentery is endemic

It is desirable that test cases used in the clinical trial of drugs should have ulceration which can be viewed through *the sigmoidoscope and active E histolytica* demonstrable in the stools or in material obtained directly from the ulcers Many such cases were available in Great Britain during World War II among service personnel invalided from overseas but since the war they have become com paratively scarce There is a wealth of clinical material in South Africa and an Amoebiasis Research Unit is engaged in therapeutic trials in Durban (Armstrong Wilmot and Elsdon Dew 1950)

The laboratory testing of drugs against *E histolytica* both *in vitro* and in animals is complicated because bacteria are inevitably present and such tests may give a false impression Any method for assessing the direct action of a compound upon the amoeba must take into account the effects of that substance on all concomitant bacteria *E histolytica* is a strict anaerobe and is able to live in ordinary mixed cultures exposed to air because the accompanying aerobic bacteria remove the oxygen If the essential aerobes for instance *Escherichia coli* or *Staphylococcus aureus* are killed the amoebae die (Dobell 1947)

Amoebicidal drugs

Emetine —Although many substances are lethal to *E histolytica* no drug has yet been found which compares with emetine in this respect Amoebae are unable to survive in concentrations of even *less than 1 5 000 000 of emetine hydrochloride* Given parenterally emetine usually has a dramatic and curative action in amoebic *hepatitis and other secondary lesions* In intestinal amoebiasis however emetine injections give *poor results and for this reason emetine bismuth iodide (EBI)* a fine powder administered orally in gelatin capsules was introduced in 1918 by Dobell who led the investigation of a large series of convalescent carriers during World War I A single course of emetine bismuth iodide 3 grains given each evening for 12 days was found to cure 95 per cent of these carriers however the cure rate in cases with active ulceration is much lower Emetine treatment must be carefully supervised on account of toxic effects on the myocardium which may cause a fall of blood pressure and alterations in conductivity Emetine bismuth iodide often causes nausea and occasionally vomiting and diarrhoea with dark stools occurs during treatment Emetine periodide and auremetine a compound

of the periodides of emetine and the dye auramin are less likely to cause nausea and vomiting but these later preparations have not been generally adopted

Iodine-oxyquinoline compounds—These are amoebicidal in strong concentrations and drugs belonging to this group have been used widely in the treatment of intestinal amoebiasis for the past 30 years Most observers agree that Diodoquin (di iodohydroxyquinoline) is the most satisfactory of these preparations It was produced in America in 1935 and is an almost insoluble compound which contains 64 per cent iodine Morton (1945) obtained 77 per cent cures in a series of cases of chronic amoebiasis treated with Diodoquin alone The standard course of treatment consists of 3 tablets (0 2 gram each) 3 times daily by mouth for 20 days and this has largely replaced the more complicated course of treatment with retention enemas of chiniofon which had gained favour previously Diodoquin is non toxic but occasionally pruritus ani occurs during treatment and on rare occasions the drug may cause diarrhoea

Arsenical compounds—Since salvarsan was first used in the treatment of amoebiasis in 1915 various synthetic arsenical compounds have been produced for oral administration Stovarsol (Acetarsol *B P*) which is $\frac{1}{10}$ as amoebicidal as emetine and carbarsone may give symptomatic relief but they are unsatisfactory when used alone in the treatment of amoebiasis Milibis (bismuth glycolylarsanilate) the most recent of these compounds was evolved in Germany during World War II This drug appears to be useful in the treatment of carriers but it is not recommended for the treatment of active amoebiasis

Conessine—This alkaloid which is derived from *Holarrhena floribunda* a shrub allied to kurchi the ancient Indian remedy for dysentery is favoured by some French workers for the treatment of intestinal and hepatic amoebiasis Conessine may produce toxic reactions and these include psychosis and blood dyscrasias

Combinations of amoebicidal drugs—Since none of the amoebicidal drugs is entirely satisfactory when given alone in the treatment of intestinal amoebiasis many combinations of these drugs have been employed Prior to the advent of the antibiotics most authorities relied upon a blunderbuss attack on *E histolytica* lasting several weeks using emetine emetine and bismuth iodide chiniofon and arsenicals in various combinations Manson Bahr (1944) found that the most efficacious form of treatment consisted of a standard course of emetine and bismuth iodide reinforced with retention enemas of chiniofon Armstrong Elsdon Dew and Marot (1949) obtained 80 per cent immediate successes with a combination of diodoquin and emetine and bismuth iodide

Antibiotics

Penicillin—During World War II many severe cases of chronic amoebic dysentery were invalided home after receiving repeated courses of anti amoebic drugs without success in some instances for periods as long as 2 years They were bedridden and cachetic with frequent foul stools containing blood and many amoebae Bacterial infection was believed to be playing an important part in these cases and penicillin was tried with dramatic effect In all cases it led to an eventual cure and in some it was life-saving (Hargreaves 1945) Symptomatic relief was obtained within a few days and on sigmoidoscopy ulcers were seen to heal rapidly Penicillin was found to have no effect upon *E histolytica in vitro* and amoebae were found to

persist in the stools when ulceration had healed therefore this treatment was followed up with a course of emetine and bismuth iodide In addition in order to combat organisms which were not sensitive to penicillin succinylsulphathiazole was given by mouth during the penicillin treatment Armstrong Elsdon Dew and Marot (1949) found that treatment with penicillin and sulfasuxidine was more effective than emetime Subsequently they obtained 95 per cent immediate successes with a course of treatment consisting of penicillin 300 000 units intra muscularly and sulfasuxidine 15 grams by mouth daily for 7 days followed by emetine 10 daily injections of 1 grain subcutaneously combined with a standard 20 day course of Diodoquin 3 tablets 3 times daily There were 56 patients in this series all with demonstrable ulcers and vegetative amoebae Blanc and Siguier (1950) have treated 200 cases of chronic amoebiasis with penicillin and sulphaguanidine combined with emetine injections Their immediate results were also very good but only 50 per cent of their patients were per manently cured by this treatment and they now follow it with arsenicals and Diodoquin

The newer antibiotics—Bacitracin was the first of the newer antibiotics to be tried in the treatment of intestinal amoebiasis This is a polypeptide compound which is nephrotoxic when given parenterally but when taken by mouth it is not absorbed from the alimentary tract Its main effect is against Gram positive bacteria *In vitro* bacitracin is only slightly active against *E histolytica* but *in vivo* it is highly effective in clearing amoebae from weaned rats which have been inoculated intracaecally with vegetative *E histolytica* and it has proved successful in human cases of amoebic dysentery In a personal trial 11 cases were treated with 2 tablets (10 000 units bacitracin each) by mouth every 6 hours for 10 days They all had demonstrable ulcers with vegetative *E histolytica* and in all cases there was rapid symptomatic relief and healing of the ulcers and the stools became free from amoebae Six patients have been followed up for a year and appear to be cured 3 relapsed after several months and 2 have not been seen again The 3 relapsing cases responded again to bacitracin and after this a standard course of Diodoquin was given They have remained free from infection for periods up to 9 months Most Miller and Grossman (1950) report 66 per cent cures following bacitracin treatment in a series of 51 patients of whom 13 were asymptomatic 30 mildly symptomatic and 8 moderately or seriously ill These observers found that aureomycin given in doses of 1–2 grams daily for 10 days was effective in clearing 32 asymptomatic or mildly symptomatic cases but failed in 1 severe case Armstrong Wilmot and Elsdon Dew (1950) have found that 94 per cent of their cases of amoebic dysentery with demonstrable ulcers responded to aureomycin and they consider that aureomycin is the most effective single drug which they have used However they report a high relapse rate during the first month after treatment Most and Van Assendelft (1950) report that terramycin in daily doses of 1 and 2 grams by mouth for 10 days has eliminated the amoebae in all of a series of 21 infected individuals but the severity of the disease in these cases is not stated The early results with terramycin in severe cases observed personally have been equally satisfactory as have those obtained with bacitracin and aureomycin

The ultimate test of the amoebicidal power of drugs which are absorbed

from the intestinal tract lies in the treatment of liver abscesses uncomplicated by bacterial infection Here aureomycin and terramycin are ineffective their anti amoebic action being secondary to their bacteriostatic effect. Before the status of the newer antibiotics can be assessed properly in the treatment of intestinal amoebiasis larger series of cases must be followed up for longer periods However it is likely that their eventual role will be in combination with amoebicidal drugs.

General treatment

If there are severe dysenteric symptoms the patient may only be able to tolerate fluids but a high calorie diet should be given as soon as possible The maintenance of good nutrition and attention to the vitamin intake especially the B complex, being more important than the need for a low residue diet

Post-dysenteric symptoms

Residual symptoms of colonic irritability with a brisk gastro-colic reflex may persist in some patients for many months following severe dysentery the colon showing a tendency to spasm at sigmoidoscopy Such symptoms usually respond to treatment with anti-spasmodic drugs and a pill containing dry extract of belladonna ¼ grain and codeine sulphate ¼ grain taken after breakfast has often proved effective Sometimes there may be constipation and this can be relieved by liquid paraffin or agar emulsion

AMOEBIASIS OF THE LIVER

Amoebic abscess and the prodromal stage of hepatitis are the most important metastatic lesions The classical clinical picture of hepatic amoebiasis should not as a rule be overlooked particularly when the condition develops during or following amoebic dysentery However there may be no previous history of dysentery and there may be an incubation period of many years in some patients amoebic abscess has occurred more than 30 years after their return home from the tropics Again the disease may simulate many other conditions or may present obscure symptoms such as vague fever with no localizing features Occasionally liver abscesses do not give rise to symptoms healed lesions have been found at autopsy and calcified abscesses have been discovered incidentally on radiological examination

Diagnosis

The onset may be insidious or acute the symptoms varying from chronic ill health to sudden episodes suggestive of right basal pneumonia or acute abdomen Fulminating cases in which the whole liver is riddled with collections of pus, are encountered on rare occasions usually in endemic areas and in association with severe malnutrition Remittent fever rising to 103 or 104 F at night is a common feature in acute cases but in more chronic ones it is less marked and may subside even in the presence of an abscess A low-grade fever with night

sweats may be the only symptom Leucocytosis with a considerable increase in polymorphonuclear cells is often found in patients with high fever but there is no hard and fast rule and a normal leucocyte count does not eliminate the possibility of liver abscess The complexion usually becomes muddy but frank jaundice is rare Dull pain and a sensation of heaviness in the right hypochondrium are common symptoms the pain being aggravated by any jarring movement so that the patient may support his enlarged tender liver with his hands when he walks There may be a dry cough and diaphragmatic pain which is referred to the right shoulder In abscesses of the left lobe of the liver the pain may be referred from the diaphragm to *the left shoulder*

The upper part of the right lobe is the most common site of abscess formation and for this reason physical signs at the base of the right lung are of particular significance in patients who have lived in the tropics Suggestive signs are diminution of movement and of vocal fremitus upward extension of the liver dullness feeble breath sounds and pleural friction Later the lower intercostal spaces may bulge and tender spots may be elicited An abscess may rupture suddenly through the diaphragm into the lung when the contents are usually coughed up as pink or chocolate coloured pus or the process may be more gradual producing a chronic basal condition with a sero purulent pleural effusion and clubbing of the fingers which may be diagnosed erroneously as bronchogenic carcinoma The differentiation from subphrenic abscess may be particularly difficult *E histolytica* may be present in the faeces but on the other hand repeated stool examinations may prove negative Radiological examination of the chest is often diagnostic The earliest sign is diminished movement of the right side of the diaphragm on screening Later local bulging may be seen in the postero anterior view or there may be elevation and fixation of the whole of the right diaphragm the outline of which may be blurred (*see* Fig 219) The right cardiophrenic angle may be obliterated and a basal effusion may be present If a liver abscess has ruptured into the lung a cavity may be visible containing a fluid level (*see* Fig 220) This may also be seen radiologically after aspiration of the abscess as it is common for some air to leak in and replace some of the withdrawn fluid To make certain of this air can be introduced purposely so that the abscess cavity can be outlined accurately (*see* Fig 221) and its subsequent progress watched in serial films

Less frequently an abscess may form in the lower part of the right lobe of the liver in the left lobe or in the quadrate lobe giving rise to abdominal symptoms A right sided abscess may be mistaken for a renal tumour An abscess of the left lobe may present as a tumour in the epigastrium or in the left hypochondrium where it may be mistaken for the spleen When such abscesses form rapidly they cause peritoneal irritation with acute abdominal symptoms when they are usually diagnosed at emergency laparotomy They may rupture into the peritoneum sometimes with fatal results or into the stomach or bowel when spontaneous recovery may ensue

In the absence of a dependable complement fixation test the diagnosis of many suspected cases of metastatic amoebiasis has rested upon a therapeutic test with emetine injections and this procedure has often proved life saving

FIG 219—Amoebic liver abscess (*a*) before and (*b*) after aspiration. There is elevation of the right side of the diaphragm with blurring of the outline due to pleural involvement

(*a*)

(*b*)

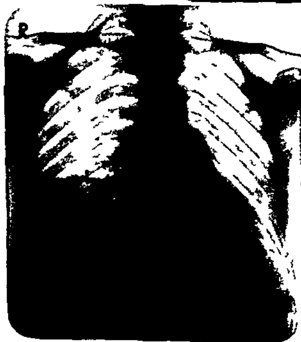


Fig 220—(a) Antero-posterior and (b) lateral views of an amoebic liver abscess which has ruptured into the lung part of the contents being expectorated This lesion resolved completely following emetine treatment





(a)



(b)

FIG 221—Large amoebic abscess of liver (a) before and (b) after aspiration and air replacement There is almost complete excavation of the right lobe (*By courtesy of The Practitioner*)



(a)

FIG 220—(a) Antero-posterior and (b) lateral views of an amoebic liver abscess which has ruptured into the lung part of the contents being expectorated This lesion resolved completely following emetine treatment



(b)

resistant to emetine The fever subsided rapidly amoebae disappeared from the discharge in a few days and the wound healed within 2 weeks Conan and his colleagues (1950) report the successful treatment of two patients with hepatic amoebiasis who developed considerable pleural effusions They were both cured without aspiration Other observers have confirmed the value of chloroquine in hepatic amoebiasis The dosage recommended at present consists of 0 6 gram (base) once daily by mouth for 2 days followed by 0 3 gram (base) daily for 2 to 4 weeks Chloroquine is superior to emetine and conessine as regards toxicity but the patient should be kept under medical supervision throughout treatment for occasional toxic effects have been noted consisting of headache nausea or vomiting pruritus disturbance of accommodation excitability and insomnia Meanwhile preliminary trials with another 4 amino quinoline compound sontoquine naphthoate indicate that this may prove equally effective

OTHER PROTOZOAL INFECTIONS

Compared with *E histolytica* the other intestinal protozoa are of little medical importance Four amoebae in addition to *E histolytica* may inhabit the intestinal tract of man These are *Entamoeba coli Endolimax nana Iodamoeba buttschlii* and *Dientamoeba fragilis* There is no evidence that any of them are pathogenic to man although at times a heavy infection with *D fragilis* has been associated with diarrhoea *E coli* is the most important for it is often confused with the commensal form of *E histolytica* and on rare occasions human cases have been reported with *E coli* containing red blood corpuscles (Hoare 1949)

Balantidium coli a ciliate which is the largest of the human intestinal protozoa has a world wide distribution but is most common in countries with temperate climates The natural host of this parasite is the pig in which it lives commensally in the lumen of the intestine Man is infected by food or drink contaminated with the faeces of infected pigs or by conveying cysts from the hands to the mouth when handling pigs in farms and slaughter houses In man also the ciliate usually lives commensally in the lumen of the large intestine cysts being passed in the stools Occasionally however it may invade the mucosa and submucosa producing ulcers which resemble amoebic lesions and causing diarrhoea or dysentery (balantidial dysentery) when active ciliates are found in the stools Stovarsol and chiniofon have been used with success in the treatment of this infection

Giardia intestinalis (*G lamblia*) is a common flagellate which lives in the small intestine of man and many other animals throughout the world As a rule only cysts are passed but when diarrhoea occurs the stools may contain free flagellates *Giardia* attaches itself to the mucous membrane of the duodenum and ileum living on the intestinal contents Its pathogenicity has not been proved but it is widely believed that it may cause mechanical irritation and interfere with the absorption of fats It is not uncommon for cases of diarrhoea and steatorrhoea in which a heavy giardial infection is found to respond to treatment with mepacrine (Atebrin) which has a specific effect upon the parasite A dosage of 0 1 gram 3 times daily for 5 days is usually adequate As might be expected giardial infection was rare during World War II when mepacrine was used as a routine for the suppression of malaria *Trichomonas hominis* is another common intestinal flagellate of man

Treatment

Emetine

The dramatic response of most cases of amoebic hepatitis to subcutaneous injections of emetine hydrochloride 1 grain daily for 10 to 12 days is well known In a few days the pyrexia subsides the hepatic pain and tenderness are relieved and within a week or two the leucocyte count and sedimentation rate return to normal In the absence of tumour formation or definite radiological signs it is difficult to distinguish clinically between hepatitis and liver abscess but small abscesses usually resolve following emetine treatment In the case of large abscesses emetine usually gives symptomatic relief and it is customary to start the course of injections a few days before aspiration is carried out Liver abscesses as a rule are sterile bacteriologically but secondary infection may occur in abscesses which have ruptured or sometimes following aspiration in which case antibiotics must be given in addition to emetine If *E histolytica* is found in the stools the emetine injections must be followed by a course of treatment for the bowel infection

Aspiration—In the case of the usual abscess in the upper part of the right lobe the liver is explored under local anaesthesia through one of the lower intercostal spaces in the posterior or mid axillary line or at the point of maximum tenderness A long needle is necessary and its bore should be wide as the pus is usually creamy in consistency The average amount of pus aspirated is about half a pint although several pints may sometimes be obtained The pus is odourless and varies in colour being yellow pink or resembling anchovy sauce depending upon the amount of blood and degenerated liver tissue present Amoebae are not usually present in the pus itself but in the edge of the infected lesion At the end of aspiration 1 grain of emetine hydrochloride should be injected into the cavity The course of emetine injections is completed and both aspiration and emetine are repeated if pus re accumulates Sometimes pus is not located and the hepatic enlargement subsides completely with emetine treatment Again only small beads of pus may be with drawn at varying depths suggesting multiple small foci and here again emetine by itself has effected a cure Abscesses of the left lobe may also be aspirated if they point in the epigastrium but laparotomy and surgical drainage are usually necessary in the case of liver abscesses presenting abdominally

New amoebicides

Until recently emetine was unchallenged in the treatment of metastatic amoebiasis resistant cases being very uncommon and the only disadvantage being the toxicity of the drug Conessine which has gained favour among some French authorities is not such a potent amoebicidal drug as emetine and is also a toxic compound Conan s observation in 1948 that chloroquine which is comparatively non toxic was effective in the treatment of hepatic amoebiasis has proved to be of great importance This 4 amino quinoline compound which was produced during World War II as an anti malarial drug is amoebicidal in high concentrations When given by the mouth it has little effect upon intestinal amoebiasis but it is rapidly absorbed from the intestinal tract and accumulates in the tissues particularly the liver where amoebicidal concentrations of the compound are soon reached Murgatroyd and Kent (1948) gave chloroquine to a case of liver abscess which had been draining pus with *E histolytica* for over 4 months and which had proved

subsequently attaining maturity in the caecum Thus it is wise to use an anthelmintic drug as a routine in addition to hygienic measures and to apply an ointment such as nupercainal locally at night to relieve any pruritus and to interfere with ovi position in the perianal area Gentian violet is the drug of choice in a dosage of 1 grain 3 times daily for adults and 1/6 grain for each year of age 3 times daily in the ca e of children This is usually given for 2 periods of 8 days with an interval of 1 week

Ancylostomiasis

Many ex prisoners of war returning from the Far East in 1945 were found to be infected with hookworms but whether they were treated or not these men should be free from infection now since ancylostomes only live for a few years Most infections occurring in servicemen during World War II were mild but severe cases were seen at times occasionally producing alarming symptoms For instance a young man on leave from Burma suddenly collapsed and was found to have an extreme degree of anaemia with leucocytosis and an eosinophilia of 90 per cent He was sent to hospital with a tentative diagnosis of eosinophilic leukaemia Large numbers of ancylostome ova were found in his stools and after blood transfusions he was treated with tetrachlorethylene and made an uneventful recovery Six weeks previously in Burma he had been treated for dermatitis involving the whole of his back which came on after he had sunbathed on a mossy river bank The true nature of this lesion was not suspected but undoubtedly the rash was caused by the penetration of the skin by innumerable larvae Tetrachlorethylene is now the drug of choice for ancylostomiasis A dose of 4 millilitres is administered in capsules by the mouth first thing in the morning on an empty stomach and followed after an hour by a saline purge

Strongyloidiasis

Many cases of infection with *Strongyloides stercoralis* are still encountered in Great Britain in ex prisorers of war from the Far East for this condition may persist for many years Recurrent urticarial eruptions are a common symptom and examination of the stools usually reveals the presence of motile larval worms which sometimes cause intense pruritus ani The adult female worms penetrate deeply into the intestinal mucosa and for this reason strongyloidiasis has resisted all forms of treatment devised up to the present

Schistosomiasis

One of the most interesting advances in the field of helminthology has been the introduction of Miracil D a non metallic compound which is a derivative of thioxanthane for the treatment of schistosomiasis This drug was developed in Germany during World War II and was found to be effective against schisto somiasis in animals It is a yellow powder which is soluble in water and rapidly absorbed from the intestinal tract When it is given orally to animals experimentally infected with *Schistosoma mansoni* and *Schistosoma haematobium* it causes viable eggs and symptoms to disappear and it is lethal to the adult worms Initial clinical trials proved encouraging (Blair Hawking and Ross 1947) but up to the present the results in *S mansoni* infections have been less satisfactory than in *S haematobium*

It lives in the large bowel and occasionally ingests red blood corpuscles Its pathogenicity is also doubtful but here again heavy infections are sometimes found in association with diarrhoea which subsides when the parasites are cleared Stovarsol is usually effective in a dosage of 4 grains twice daily by mouth for 10 days

Coccidia are common intestinal parasites in lower mammals and infection with *Isospora belli* (*I hominis*) sometimes occurs in man in tropical and subtropical countries giving rise to colitis The diagnosis is based on the finding of oocysts of *Isospora* in the stools Treatment with large doses of bismuth salicylate has been found satisfactory

HELMINTHIC INFECTIONS

Whereas parasitic worms are an important cause of morbidity throughout the world in Great Britain helminthic diseases have become comparatively uncommon *Enterobius vermicularis* the threadworm is the only intestinal worm which is en countered with any frequency In Great Britain infections with *Ascaris lumbricoides* the roundworm are rarely heavy enough to cause the intestinal symptoms which are common in the tropics Trichinosis has practically disappeared since World War II and the consequent shortage of pork but an increase has been noticed in the incidence of *Cysticercus bovis* the larval stage of *Taenia saginata* in beef at routine inspections at abattoirs although there have been no reports of any increased frequency of human infection with the adult worm Incidentally a person with a tapeworm may not always be aware of its presence Hurst and Robb Smith (1942) described the case of a woman who harboured *Taenia saginata* for some 25 years without noticing segments in her stools and eventually died of tapeworm enteritis *Taenia solium* has been practically extinct in Britain for many years since *Cysticercus cellulosae* the larval stage is readily detected by meat inspectors in the flesh of the pig which tends to be heavily infected An individual harbouring *Taenia solium* is a particular danger to the community and also to himself for ingestion of the ova which are passed in the faeces may give rise to cysticercosis in man Most of the cases detected in Great Britain developed epileptiform attacks after living in India 26 per cent gave a previous history of tapeworm and therefore were probably cases of auto infection (Dixon and Hargreaves 1944)

Enterobiasis

Threadworm infection can usually be cured without using anthelmintic drugs if re infection is prevented Until recent years it was believed that this could be accomplished by preventing the transference of ova from the perianal skin to the mouth by means of strict hygienic measures such as scrupulous cleansing of the hands and perineum and the wearing of clean tightly fitting drawers each night and in addition rectal douches to remove gravid female worms However occasional cases were encountered where such measures failed These resistant cases have been explained by Schuffner and Swellengrebel (1944) who have described the process of retrofection in which eggs laid in the perianal region sometimes hatch out the larvae crawling back through the anus during the night and

subsequently attaining maturity in the caecum Thus it is wise to use an anthelmintic drug as a routine in addition to hygienic measures and to apply an ointment such as *nupercainal* locally at night to relieve any pruritus and to interfere with ovi position in the perianal area Gentian violet is the drug of choice in a dosage of 1 grain 3 times daily for adults and 1/6 grain for each year of age 3 times daily in the case of children This is usually given for 2 periods of 8 days with an interval of 1 week

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infections although some definite cures have been obtained in *S mansoni* dysentery One great advantage of the drug over the trivalent antimony compounds is that it is given by mouth and thus is easy to use in native dispensaries The compound is marketed in Great Britain under the name of Nilodin in 200 milligram tablets both coated and plain The uncoated tablets appear to be preferable and the optimum dosage has yet to be determined The minimum effective dose of nilodin appears to be 60 milligrams per kilogram body weight given in divided doses over a period of 3–6 days Side effects have occurred in some patients consisting of nausea abdominal discomfort sweating muscular twitching dizziness and insomnia These symptoms are rarely severe and soon subside after treatment is completed

REFERENCES

Armstrong T G Elsdon D w R and Marot R J (1949) *S Afr med J* 23 369
— Wilmot A J and Elsdon D w R (1950) *Lancet* 2 10
Blair D M Hawking F and Ross W F (1947) *Ibid* 2 911
Blanc F and Siguier F (1950) *L Amibiase* Paris Expansion Scientifique Française
Conan N J (1948) *Amer J trop Med* 28 107
— Head J A and Brewer A E (1950) *Trans R Soc trop Med Hyg* 43 659
Dixon H B F and Hargreaves W H (1944) *Quart J Med* 13 107
Dobell C (1919) *The Amoebae Living in Man* London Bale
— (1947) *Ann Soc belge Med trop* Liber Jubilaris J Rodhain
— Gettings H S Jepps M W and Stephens J B (1918) *Spec Rep Ser med Res Coun* No 15
Hargreaves W H (1945) *Lancet* 2 68
Hoare C A (1949) *Handbook of Medical Protozoology* London Baillière Tindall & Cox
— (1950) *Brit med J* 2 238
Hurst A and Robb Smith A H T (1942) *Guy s Hosp Rep* 91 58
Losch F (1875) *Arch path Anat* 65 196
Manson Bahr P (1944) *Lancet* 2 718
— (1947) *Trans R Soc trop Med Hyg* 41 73
Morgan C N (1944) *Brit med J* 2 721
Morton T C (1945) *Ibid* 1 831
— (1946) *Ibid* 1 890
— Neal R A and Sage M (1951) *Lancet* 1 766
Most H Miller J W and Grossman E J (1950) *Amer J trop Med* 30 491
— and Van Assendelft F (1950) *Ann N Y Acad Sci* 53 427
Murgatroyd F and Kent R P (1948) *Trans R Soc trop Med Hyg* 42 15
Rees C W (1950) *Gaz med Fr* 57 835
Samuel E (1948) *Brit J Radiol* 21 625
Schuffner W and Swellengrebel H H (1944) *Zbl Bakt* 151 114
Wenyon C M (1947) *Trans R Soc trop Med Hyg* 41 55

CHAPTER 26

BACTERIOLOGY IN RELATION TO THE ALIMENTARY TRACT

Joan Taylor

It is known that the faecal flora can vary within very wide limits in healthy persons but no list can be given of organisms always present in normal faeces In addition little is known of the variation in the flora found at different levels of the bowel or of the variation found in individuals living in different localities or climates It has been suggested that any sudden gross change in the bacterial flora of the intestine in any single individual may give rise to intestinal symptoms but the small amount of work done on this point suggests that only minor symptoms may arise in this way if unaccompanied by the presence of accepted pathogens The interpretation of this type of investigation is difficult because of the known differences in susceptibility of individuals to known pathogenic bacteria which it may be assumed is reflected in their susceptibility to changes in the normal intestinal flora

The majority of the bacteria in this field have been studied from the point of view of their relationship to intestinal disorders but more recently the intestinal tract has come to be regarded as the possible portal of entry for infective processes affecting other parts of the body such as the central nervous system in poliomyelitis or the liver in infective hepatitis The invasion period of these diseases may be accompanied by intestinal symptoms though it is not known whether these are of local or central origin Some intestinal diseases such as the enteric fevers are characterized by a generalized spread of the infecting organism throughout the body which later becomes localized in the intestine in these diseases as well as in poliomyelitis a history of mild intestinal upset occurring at the time of invasion may be elicited the patient remaining healthy between this invasion period and the onset of the classical disease It is proposed to discuss the bacterial and virus diseases of which the main effects are on the intestine and to omit those in which intestinal disorder is but a minor part of the classical disease

Many infections of the intestinal tract are classified as food poisoning suggesting that the infective agent enters the body *via* food or drink This is commonly true of the salmonella group of organisms some of the paracolon group and of toxic food poisoning yet there are some diseases not uncommonly due to infected food which are not classified in this way A number of outbreaks of dysentery has been caused by infected milk and foods such as pease pudding responsible for the outbreak of Sonne dysentery described by Scott (1934) yet dysentery is not regarded as food poisoning Nevertheless the term food poisoning is well known and will be used to describe diseases due to the multiplication within the

body of pathogenic organisms contained in food commonly known as infectious food poisoning and to those due to the ingestion of food containing pre formed bacterial toxin toxic food poisoning

FOOD POISONING

The various types of food poisoning have many points in common though all age groups are affected the majority of fatal cases occur in the very young and in the old

Table I shows the number of deaths from salmonella infection in the United Kingdom classified in relation to the age of the patient In toxic food poisoning also deaths occur in old persons and in those suffering from debilitating diseases

TABLE I

Age-years	0–4	5–9	10–19	20–29	30–39	40–49	50–59	60–69	over 70
No of cases	253	62	93	85	72	68	55	43	33
No of deaths	6	0	0	0	1	4	4	5	8

(From Taylor 1951)

A number of organisms are capable of forming true exotoxins which act on the intestine The enterotoxin is formed in the food during the period of multiplication of the bacteria outside the body As the disease is due to the ingestion of a pre formed toxin the period between the ingestion of the food and the onset of symptoms is short as compared with the incubation period of infectious food poisoning Table II including chemical for purposes of comparison shows the average incubation periods of the various types of food poisoning

TABLE II
INCUBATION PERIOD OF FOOD-POISONING

Chemical	Bacterial toxin: Staphylococcus	Bacterial toxin: *Cl welchii streptococci*	Infectious
0 30 minutes	2 hours	12 hours	20 hours

The investigation of food poisoning should be approached both from the epidemiological and from the laboratory angle It is believed that though a patient with classical symptoms of food poisoning appears to be an isolated case inquiry will usually reveal the presence of related cases The patients symptoms in a single outbreak vary very considerably due to differences in the amount of infected food eaten and to variations in individual susceptibility It has also been suggested that patients having a high acid content in the gastric juice are less susceptible There is some evidence suggesting that an attack of either toxic or

infectious food poisoning may confer some degree of transient immunity to a second similar attack. The laboratory investigation aims at the isolation and identification of the causal organism both from the patients at risk and from the food. The types of material most suitable for investigation are faeces and vomit but may also include an examination of the patient's serum for the presence of specific antibody production.

The widespread use of sulpha drugs and antibiotics may cause very great changes in the flora of the intestine so that the primary investigation of faeces or other material from the intestine must be undertaken before the beginning of any such treatment if reliable data on the bacterial flora are to be obtained.

A comparison between the main symptoms of toxin and infectious food poisoning are shown in Table III.

TABLE III

MAIN CLINICAL SIGNS AND SYMPTOMS OF FOOD POISONING

Infection type	*Toxin type*
Acute onset	Acute onset
Malaise	Nausea
Vomiting	Vomiting
Abdominal pain	Abdominal cramps
Diarrhoea	Diarrhoea
Pyrexia	Weakness
	Collapse—condition of shock
	Temperature normal—sub-normal
Incubation period 4-48 hours	Incubation period 1-12 hours
Average 20 hours	Average 2 hours
Duration 2-5 days	Duration 1 day

Toxin type

Enterotoxin is produced by some strains of *Staph. pyogenes* and may be produced by some strains of *Cl. welchii* and streptococci. *Cl. botulinum* produces an exotoxin which affects the central nervous system.

A number of other organisms are also believed to cause this type of disease as many outbreaks suggestive of toxic food poisoning have occurred from which no known enterotoxin producing organisms have been isolated. Organisms such as *Proteus vulgaris*, *Bact. coli* and others have been isolated from the suspected food but there is no information which shows whether their action is due to an enterotoxin or the living organism. These organisms have not been shown to cause disease in animals but on epidemiological grounds it is possible that they may affect man. When these organisms have been incriminated they have been present in the food in very large numbers and it is possible that during the period of their multiplication irritating substances are produced from the food. Some observers have been able to cause intestinal symptoms in monkeys by giving them food infected with *Proteus* or *Bact. coli*; others have failed to repeat these results. It is probable that special conditions for bacterial growth and the type of food will influence the production of these irritating substances, such conditions being as yet unknown.

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Some of the ways in which food may be infected have been mentioned but the type of food varies a great deal and includes beef tongue lamb bacon sausage meat pies meat sandwiches cake potato salad ice-cream and trifle When conditions of temperature moisture and environment are suitable the staphylococci multiply and form enterotoxin In some outbreaks a large amount of food has been allowed to cool gradually overnight so enabling the formation of the enterotoxin Some outbreaks have been due to re heated food and it is b lieved that though the staphylococci present have been killed or reduced in numbers the enterotoxin has withstood this treatment

Little mention has been made of sporadic cases of staphylococcal food poisoning these are known to occur but as patients recover rapidly many fail to consult their practitioner undoubtedly the majority are never recorded During 1949 of 97 incidents (sporadic cases outbreaks family outbreaks) recorded only 8 were sporadic cases

Denys (1894) first reported that staphylococci were able to produce a toxic substance capable of irritating the gastro-intestinal tract Many similar observa tions have been made during the intervening years Dolman and others (1936) showed experimentally that some strains of staphylococci when cultured under certain specified conditions were able to form a toxin which was present in a bacteria free filtrate of the medium in which the organisms had been cultured The filtrate when ingested by human volunteers caused the symptoms of toxic food poisoning In addition this toxic filtrate caused vomiting in kittens when injected intraperitoneally Unfortunately the kitten test is not specific for the enterotoxin and the most reliable test remains that on human volunteers Staphylococcal enterotoxin may withstand boiling for half an hour though this treatment will kill the staphylococcal organisms so it is possible to have a toxic food from which few or no staphylococci can be isolated It has been found that only certain strains of staphylococci are capable of forming enterotoxin they also have the property of clotting plasma (coagulase positive) nevertheless not all coagulase positive staphylococci are able to form enteroxin

Clostridium welchii

Some outbreaks of food poisoning are recorded having an incubation period of about 12 hours midway between that of staphylococcal food poisoning and salmonella infection A number of observers have isolated anaerobic spore bearing bacilli from the suspected food McClung (1945) records three outbreaks of food poisoning from which he isolated the anaerobic *Cl welchii* All three outbreaks had this intermediate incubation period he was able to reproduce the clinical disease in a human volunteer who ate food infected with *Cl welchii* but with no other organisms Neither the types of *Cl welchii* isolated nor the toxins produced were described

The symptoms are intestinal cramps and usually profuse diarrhoea sometimes accompanied by nausea and vomiting The patients have usually recovered in 24 hours Examination of stool from affected patients revealed the presence of heat resistant *Cl welchii* spores in 70–100 per cent whereas from a control group of normal persons and those suffering from food poisoning due to other causes *Cl welchii* have been isolated from only 4 per cent.

Staphylococcus pyogenes

The most important of the enterotoxin producing organisms are the coagulase positive staphylococci The illness usually starts about 4 hours but may vary from 1–7 hours after the food has been eaten The onset of symptoms may be extremely sudden as reported by Williams and others (1946) who described 3 outbreaks affecting 40 500-600 and more than 58 persons respectively The symptoms are abdominal pain sometimes of a cramp like nature severe vomiting followed by diarrhoea and often accompanied by a feeling of weakness which may result in collapse Pallor is marked and the skin is cold and sweating in severe cases The temperature rarely rises above 99 F and may be subnormal The respirations and pulse rate and volume vary with the degree of collapse Many descriptions have compared this disease with that of sea sickness as in both diseases the more severely ill patients are in such a state of collapse that they are unable to stand and do not care whether they live or die In spite of the severity of the disease recovery is rapid and usually complete in 24 hours It has been said that no case is ever fatal but a few deaths have been recorded in very young or old persons and in those suffering from such debilitating conditions as heart disease Though the symptoms may be severe many cases are relatively mild and patients may complain of little but nausea and some abdominal pain in fact all gradations of the disease may be encountered even in a single outbreak

Knowledge of the incidence of staphylococcal food poisoning has increased as a result of new methods used for isolation It is now possible to isolate these organisms from patients faeces and foods heavily contaminated with other organisms The staphylococci responsible are similar to those causing pyogenic infections They are usually orange coloured on ordinary culture media and are always coagulase positive

Of recent years staphylococci have been differentiated into serological types by the agglutination method and into phage types This latter method identifies the organism by the capacity of specific phages to cause its lysis The importance of these advances has been to increase our knowledge of the epidemiology of staphylococcal infections of all varieties including food poisoning and to detect the source of the infecting strain It is possible to type 98 per cent of strains of coagulase positive staphylococci by serological methods and 65 per cent by phage typing (Allison 1949) Identical strains of *Staph pyogenes* have been isolated from the faeces and vomit of patients from the suspected food and from the nose skin or focus of skin infection in food handlers concerned in the preparation of the food and have been shown by these means to belong to the same type During the last few years many strains of staphylococci causing food poisoning have been phage typed from such widely separated areas as Canada United States of America Egypt the Sudan and England of these 64 per cent (30 strains) belonged to one phage and serological type designated 6/47 IIIc and 25 per cent (8 strains) belonged to phage type 42 D It is not suggested that all staphylococci of the types mentioned can cause food poisoning or that other types are incapable of causing this disease Williams Smith (1948) has found type 42 D as a frequent cause of bovine mastitis and this type has been isolated from cheese More information on the occurrence of this type is needed as cheese is known to cause a number of cases of food poisoning

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for believing that the β toxin is the main intoxicating agent in this disease This result suggests that treatment with *Cl welchii* anti toxic serum type β might give good results

During survey of the normal population of Hamburg 19 cases of out 108 examined were shown to have *Cl welchii* type F in the faeces These latter strains were less pathogenic to animals than strains isolated from cases of enteritis necroticans

Clostridium botulinum

The eating of food infected with *Cl botulinum* causes the disease known as botulism The most important symptoms are not due to irritation of the gastro-intestinal tract but to a toxic effect on the central nervous system The onset of the disease is usually about 24 hours after the consumption of infected food and is characterized by vomiting constipation ocular paresis and sometimes by aphonia

There have been only four outbreaks recorded in Great Britain

Although a number of outbreaks have a high mortality rate it is known that others are mild the symptoms being transitory and the patients recovering in a few days The disease is due to the production by the organism of an exotoxin which is absorbed by the mucosa of the stomach and intestine Two main types of *Cl botulinum* have been isolated type A and B which produce separate and distinct toxins neutralized by their specific antitoxic sera The spores of *Cl botulinum* are heat resistant and may withstand boiling for from half an hour to 22 hours and may even survive a temperature of 120 C for 20 minutes It is surprising that botulism should be a rare disease as the organism is widely distributed in nature having been found in both virgin and cultivated soils A number of outbreaks of botulism in the United States of America have been due to the infection of home canned vegetables but in Europe it has usually occurred as the result of infection of meat products

It is known that many factors affect the survival germination multiplication and toxin production of *Cl botulinum* it is probable that rarely are all conditions suitable for the production of a toxic food

Streptococci

Many outbreaks of food poisoning have been described in which streptococci in large numbers have been isolated from the suspected food The symptoms have been abdominal cramps associated with nausea vomiting and diarrhoea with complete recovery usually in about 24 hours The incubation period varies in the outbreaks described from about 3 hours to about 12 hours

Streptococci isolated from suspected food have the power to cause a greenish discoloration of the medium when grown on blood agar plates and are therefore known as α haemolytic streptococci Buchbinder and others (1948) isolated a number of strains from infected foods these streptococci had the characteristics of *Str faecalis* and were similar to those isolated from normal human faeces Osler and others (1948) showed that some strains of *Str faecalis* isolated from human faeces and from food suspected of causing food poisoning were able to cause symptoms of gastro-enteritis in human volunteers

Moore (1948) isolated from suspected food an α haemolytic streptococcus

The most usual type of food causing this infection is meat dishes of various kinds in which many hours have elapsed between the primary cooking of the food and its consumption so giving time for the multiplication of organisms and toxin production Careful examination may show the presence of small bubbles due to gas production in the food which may taste slightly acid

In Great Britain a number of outbreaks due to *Cl welchii* food poisoning are believed to have occurred (Hobbs) Symptoms began 9–14 hours after taking cold or re heated meat dishes As *Cl welchii* spores resist heating for 3–4 hours the usual methods of cooking will not destroy the organism in infected food That *Cl welchii* produces a number of exotoxins is well known but as yet it has not been determined whether the clinical symptoms are due to the ingestion of the organism its toxins or both though the short incubation period is suggestive of toxic food poisoning In one outbreak in Great Britain a number of deaths occurred in old debilitated persons Although the food poisoning syndrome appears to be very different from enteritis necroticans it is possible that this difference is one of severity rather than the occurrence of two distinct diseases

An intestinal disease believed to be due to *Cl welchii* is enteritis necroticans a number of cases of which have been described by Beckerman and Laas (1946) and Zeissler and Rassfeld Sternberg (1949) The latter observers state that the illness is severe and often fatal It is characterized by an acute onset with very severe abdominal pain and slight rigidity mostly in the left lower quadrant of the abdomen This is accompanied by vomiting and profuse diarrhoea resulting in dehydration which is followed by circulatory collapse and general cyanosis An increased blood urea low blood chloride indicanaemia and indicanuria may be found The temperature is slightly raised The blood picture shows a moderate leucocytosis with a marked shift to the left and the blood sedimentation rate is increased Other observers have described a disease darmbrand which appears to be similar to enteritis necroticans in which the mortality was probably 40 per cent One acute case has been described in which the patient died within twelve hours of the onset of symptoms The record of another case suggests that the disease was caused by eating infected food At autopsy there is a tube like necrosis of the intestinal mucosa commencing in the terminal part of the duodenum or the beginning of the jejunum This condition may also be found in the ileum and colon The necrosis of the mucosa may be associated with swelling of the muscle layer which itself may show areas of necrosis Films of the surface of the mucosa show the presence of many Gram positive bacilli and *Cl welchii* type F has been isolated on culture

Cl welchii type F differs from that associated with food poisoning and gas gangrene in that the rods are somewhat shorter and thicker and the spores are much more heat resistant being able to withstand boiling for 1–4 hours The *Cl welchii* group of organisms forms a number of toxins of which the α toxin plays an important part in the production of myositis *Cl welchii* type F has been shown by Oakley (1949) to form mainly the β toxin which produces a necrotic lesion on intracutaneous inoculation into guinea pigs It has been shown that the injection of cultures of *Cl welchii* type F into the lumen of the gut of guinea pigs causes an enteritis histologically similar to that seen in enteritis necroticans From these findings it may be concluded that there is strong presumptive evidence

At autopsy the mucosa of the stomach is swollen covered with slimy exudate and may show the presence of small haemorrhages if vomiting has been severe The small and large intestine may show similar changes and small superficial ulcerated areas Peyer s patches are usually somewhat swollen As a result of toxaemia the liver shows fatty changes If the patient has had septicaemia the spleen is soft and enlarged Though these changes may be seen there are many autopsies showing very few pathological lesions

Salm typhi and *Salm paratyphi A B* and C are exclusively human pathogens usually causing enteric fever but *Salm paratyphi B* may cause symptoms of acute food poisoning only in fact outbreaks have been described in which both types of disease have occurred Other salmonella species usually cause acute gastro enteritis and many cause disease in animals Both man and animals are affected by the majority of species of which some are more pathogenic to man than are others *Salm choleræ suis* infection in man has a high mortality rate in Great Britain about 50 per cent and *Salm dublin* may cause a long continued septicaemic type of disease with a fairly high mortality rate whereas the usual mortality rate (excluding the enteric group) is about 2 per cent From Table I can be seen the effect of age on the mortality rate

Organisms of the salmonella group are bacilli usually motile having flagella peritrichously arranged round the body They fail to ferment lactose a property which is used in their isolation from faeces from which the majority of organisms will ferment this carbohydrate Of recent years new solid and fluid media have been described whereby these organisms can be isolated even when present in very small numbers As a result knowledge of their distribution throughout the animal kingdoms has increased The identification of the 225 types of the genus *Salmonella* based on the investigations of White (1926) is dependent on the intricate serological identification of the component parts of heat stable somatic O complex and the heat labile flagellar H complex Many species have two separate and distinct flagellar complexes of which one is common to many species the other relatively specific The complete identification of any strain depends on the identification of the O and both H complexes only then is it possible to give a name to the type The common salmonella types can be identified in a routine laboratory but for the rarer kinds a central reference laboratory should be available A knowledge of the type is essential for epidemiological purposes but is of little value to the clinician as apart from typhoid fever there is no specific treatment

Epidemiology —The environment of human cases of salmonella infection is now subjected to a more thorough investigation than heretofore The sporadic case of salmonella infection is now believed to be rare as the same organism can usually be isolated from a number of contacts many of whom are symptomless or have merely suffered from mild intestinal upset *Further investigation often proves that a* domestic animal such as a cat or dog is also excreting the organism Vermin such as rats and mice may be healthy carriers of these organisms Recently it has been shown that artificially infected cockroaches may excrete these organisms in their faeces for periods up to 20 days A knowledge of the salmonella type is sometimes of value in tracing the probable source of infection *Salm typhimurium* as its name suggests is a cause of disease in mice It is the most ubiquitous of all the salmonella organisms having been responsible for 75 per cent of human infection in England

regarded as an atypical *Str salivarius* He showed using human volunteers that both living cultures and culture filtrates of this organism were able to produce symptoms of food poisoning and suggests that the noxious effect of the streptococci was due to a pre formed heat stable toxin

The types of food causing outbreaks have been meat meat products and milk containing foods Not all persons eating the affected food have been ill which suggests that there may be individual differences in susceptibility to this disease

Infection type

Food poisoning of the infection type is caused by the growth of pathogenic organisms within the intestine the small intestine being mainly affected but the large intestine may be involved

The symptoms of this type of food poisoning usually commence about 10–24 hours after the ingestion of the infected food but may start as early as 2 hours or as late as 48 hours after ingestion Illness commences with headache followed by nausea, vomiting and diarrhoea usually accompanied by pyrexia The faeces are usually fluid containing mucus and on microscopic examination a number of fairly normal pus cells Some patients complain of blood in the faeces but the amount is small as compared with the typical dysenteric stool

In any outbreak of food poisoning it will be found that a number of the patients have but transitory symptoms which escape notice while others remain healthy

Salmonella infection

The most important cause of this type of food poisoning is the salmonella group of organisms of which there are 225 known species including the causal organisms of enteric fever—*Salm typhi Salm paratyphi A B* and *C*

The symptoms are those described above although some patients may have the symptomatology of true enteric fever with rose spots even though infected with a salmonella species other than one of the enteric group

In some outbreaks and sporadic cases the symptoms are those of a generalized septicaemia with little or no signs of intestinal disease In these patients the organisms can be isolated from the blood In severe intestinal infections the patient becomes extremely toxic finally passing into the typhoid state before death Though these severe infections may occur it should be stressed that they are extremely rare The typical patient who suffers from salmonella food poisoning is fully recovered in about five days and during any single outbreak a number of patients will suffer no more than transitory symptoms elicited only on inquiry

Although salmonella organisms usually infect the intestinal tract they may occasionally localize in other areas In adults these organisms have caused osteomyelitis purulent arthritis pneumonia subacute bacterial endocarditis and localized abscess in the peritoneal cavity in the latter case without perforation of the bowel In young infants they have caused meningitis Hormaeche and others (1941) in Uruguay isolated these organisms from the pharyngeal exudate of a number of infants excreting the organism in faeces this fact has been confirmed by Neter and others (1950) in United States of America and Varela and Olarte (1943) in Mexico isolated a number of salmonella species from tonsils removed at operation

much less common though Wilson (1945) has shown that the bacteriological examination of eggs from pullets naturally infected with *Salm thompson* had revealed the presence of the organism in several eggs He has also shown that the ovary of the hen may be infected with *Salm typhimurium* and that this organism may be present in the egg meat (Wilson 1950) These findings are important as although infection of hens eggs is much less common than in ducks eggs the consumption of the former is greater Watt (1945) traced an outbreak of food poisoning due to *Salm montevideo* to the consumption of infected hens eggs Salmonella organisms have been isolated from 11 1 per cent of samples of American spray dried-eggs (Report 1946) and outbreaks of human infection have been traced to this source

Foods—The types of food most commonly infected are made up meat dishes custards and creams which are ideal for the growth of bacteria and are either not subjected to high temperatures in cooking or else are commonly re heated It is not uncommon to find that a food eaten when first made causes no disease but after standing or re heating causes disease showing that the ingestion of large numbers of these organisms is necessary for the production of clinical disease Little is known about the actual number of ingested organisms necessary to cause diseas Hormaeche and others (1936) found the ingestion of 2–4 million *Salm typhimurium* infected only one of four volunteers Undoubtedly not only is there a variation in the infectivity between different salmonella types but also between different strains of any one type In addition some patients are more susceptible to infection than are others

Diagnosis—The diagnosis of salmonella infection aims at the isolation of the causal organism usually from the faeces sometimes from vomit blood or other material Care must be exercised in obtaining a suitable specimen for examination before the patient has received specific treatment as the faecal flora may be very materially altered When an outbreak has occurred and the organism has been isolated from a number of patients it may be possible to determine the extent of the outbreak by finding high agglutinin titres to the organism in the serum of patients exposed to the infection It is rarely possible to determine the nature of a salmonella infection from the type of agglutinins present in the serum of a sporadic case from whom no specific organism has been isolated (excluding enteric infections)

Paracolobactrum

The *Paracolobactrum* or paracolon group of organisms is intermediate between the salmonella and dysentery groups on the one hand and the escherichia (*Bact coli*) and *Aerobacter* groups on the other Dudgeon (1921 1922) working with strains isolated from the urine of human cases of cystitis found that these organisms could be classified as haemolytic or non haemolytic Borman (1944) defined this group on biochemical reactions and Sevitt (1945) working with strains mostly isolated from cases of infantile diarrhoea classified these on the basis of their reactions on certain carbohydrates and was able to identify five major antigens by serological methods Edwards and others (1948a b) and Bruner and others (1949) have described the Arizona Bethe da and Ballerup groups of paracolobactrum classified by bio chemical and serological methods As yet there is no generally accepted classification

and Wales in 1949 for about 47 per cent of infection in chickens in the years 1933–44 (Gordon and Buxton 1946) excluding *Salm gallinarum* and *pullorum* It has also been isolated from ducks geese bovines pigs, lambs dogs canaries rats and mice during the years 1947–49 This wide natural distribution makes the identification of the source of the organism in any human infection very difficult to determine Other types relatively common in England and Wales are *Salm thompson Salm newport Salm enteritidis* and *Salm dublin* During 1943–44 *Salm thompson* was responsible for 50 of 89 outbreaks of salmonella among chickens So far it has not been possible to relate this reservoir to any human cases This organism has also been isolated from pig mesenteric glands and on occasion from American spray dried egg and a dog *Salm newport* has been isolated from pig mesenteric glands and from an outbreak of gastro enteritis in cows responsible for a milk borne outbreak of this infection *Salm dublin* is constantly being isolated from healthy cattle—Field (1948) refers to outbreaks of this infection and during 1950 strains have been isolated from the faeces of healthy cattle just prior to slaughter Nevertheless in South Wales the locality of Field s work no human cases of *Salm dublin* infection were reported during the period of investigation and no human outbreaks of *Salm dublin* infection have been notified during 1949–50 in spite of the number of infected cattle slaughtered for human consumption

Carriers —No figures showing the carrier rate in the human population are available but it is believed that in England the rate is very low

After clinical disease the patient continues to excrete the organism for a short time but is usually free of infection within 6 weeks A few may continue to excrete for many months and two babies infected during the first 10 days of life continued to excrete the organisms for 14 and 18 months respectively since when they have been negative One patient in a mental institution excreted *Salm typhimurium* for many years but may have re infected herself owing to unhygienic habits

Healthy temporary excreters of salmonellas are usually found during the investigation of contacts of a case of salmonella infection Many of these give no history whatsoever of clincial disease no information is available giving the period during which they continue to excrete these organisms but from reports on a few cases it seems probable that the period is short

Source —Little is known of the importance of human salmonella excreters in relation to infection as usually the healthy excreters have eaten the infected food This also applies to vermin trapped and investigated after an outbreak has occurred Nevertheless healthy rats and mice trapped at random may excrete salmonella organisms so must be regarded as a possible source of infection

Some naturally infected animals used for human consumption—particularly cows and pigs—will cause outbreaks of food poisoning if suffering from a generalized infection at the time of slaughter

Recently attention has been focused on eggs particularly duck eggs The duck egg may be infected as the result of infection of the ovary infection of the cloaca due to the passage of faeces or penetration of the shell after laying Ducks them selves are commonly infected with *Salm typhimurium* or *Salm enteritidis* and a number of sporadic human cases of *Salm enteritidis* and *Salm typhimurium* infection have been traced to ducks eggs Salmonella infection of hens eggs is very

from gastro enteritis This was followed by the isolation of the same type by Giles and Sangster (1948) working in Scotland Taylor and others (1949) in England Kauffmann and Dupont (1950) in Denmark Magnusson and others (1949) in Sweden Beeuwkes and others (1949) in Holland and Neter (1950) in United States of America This organism has rarely been isolated from healthy babies not in contact with the disease Thus there is good epidemiological evidence that this organism is either the cause or intimately associated with infantile and neonatal gastro enteritis from which no members of the salmonella or dysentery group of organisms have been isolated Kirby and others (1950) having isolated this specific type from two outbreaks of neonatal diarrhoea tested its pathogenicity when cultured under certain specific conditions The strain was ingested by human adult volunteers all of whom developed symptoms of diarrhoea and one of vomiting Similar experiments using strains of *Bact coli* antigenically unrelated to the diarrhoeal strains caused no symptoms Neter fed this specific type to a baby suffering from multiple congenital defects including mental deficiency The baby developed a typical attack of infantile gastro enteritis which responded to treatment with terramycin This baby failed to develop intestinal symptoms when fed with an antigenically unrelated strain of *Bact coli* isolated from its own faeces Stevenson (1950) isolated this specific type of *Bact coli* from the faeces of diarrhoea in adults though the patients concerned were suffering from other debilitating diseases It may be that these strains are pathogenic to babies but may cause symptoms only in the debilitated adult There is no evidence as yet that there is any difference in pathogenicity to animals between these and antigenically unrelated strains of *Bact coli* Since these reports another distinct serological type of *Bact coli* has been described by Smith (1949) who found it to be associated with infantile gastro enteritis

Other organisms

Many other organisms—*Proteus* group *Aerobacter* and *Pseudomonas pyocyanea* —have been described as causing intestinal disease and it is true that they have been isolated on many occasions from the faeces of both infants and adults suffering from gastro enteritis These organisms have also been isolated from healthy individuals but it is possible that their pathogenic role will not be assessed until more exact methods of identification are used Nevertheless it is probable on both epidemiological and bacteriological evidence that many of these relatively non pathogenic organisms may give rise to gastro intestinal symptoms if they are ingested in large numbers such as would occur in heavily infected foods

Viruses

Many outbreaks of epidemic diarrhoea and vomiting have been described from which no pathogenic organisms have been isolated The outbreaks occur in spring or autumn and may affect patients of all ages The onset which may be sudden usually occurs during the evening or at night Nausea and vomiting usually the initial symptoms may be severe Hargreaves (1947) described two outbreaks in which the incubation period was about three days which corresponds with other recorded outbreaks The disease is mild though deaths may occur in aged patients

within this group of organisms therefore there is little knowledge of the natural habitat or of their relation to disease in man and animals

The paracolons ferment lactose weakly late irregularly or not at all but all strains ferment glucose and usually a number of other carbohydrates Many strains may contain salmonella or dysentery antigens other strains contain *Bact coli* antigens

This group of organisms is widely distributed and frequently isolated from the faeces of normal persons in tropical countries less frequently from persons in temperate climates They are frequently isolated from faeces taken during recovery from dysenteric infections

In tropical countries paracolons have been isolated from blood taken from patients with enteric like symptoms also from the urine in patients with cystitis and from the faeces of patients with enteritis Two outbreaks of gastro enteritis probably due to the eating of infected food have been described (Hobbs 1948) in which the symptoms were reproduced by feeding the organism to human volunteers An organism of the same serological type was isolated from the faeces of patients in both outbreaks Edwards work suggests that the Arizona group causes disease in animals and occasionally in man whereas the Bethesda group is more usually isolated from the faeces of gastro enteritis in man As yet the natural distribution of these two groups is unknown so that their pathogenic role cannot be assessed To summarize certain types of paracolobactrum are able to cause human disease of the enteric type simple gastro enteritis and infection of the urinary tract It is not yet possible to assess the importance of a paracolon isolated from a sporadic case of gastro enteritis There is reason to believe that *paracolo bactrum* may be important secondary invaders in such diseases as intestinal amoebiasis and dysentery

GASTRO ENTERITIS—WITH PARTICULAR REFERENCE TO INFANTILE GASTRO ENTERITIS

Bact coli

Bact coli is accepted as being present in the faeces of all healthy adults This organism appears in the faeces usually within a few days of birth but may be absent in the faeces of breast fed infants up to 4 months of age Owing to the constancy with which *Bact coli* can be isolated from faeces it has been assumed to be non pathogenic in this situation Kauffmann (1944) published his work on the classification of *Bact coli* by serological methods this work was followed by that of Vahlne (1945) Knipschildt (1945) and Kauffmann and Dupont (1950) who investigated strains from material of human origin It has been shown that the majority of strains investigated possessed a flagellar antigen a thermostable somatic antigen and a surface antigen

The identification of *Bact coli* strains depends on the serological identification of each of these three antigens This method of identification is precise and though as yet in its infancy is giving information which may be of great value

The possible pathogenic role of certain serological types of *Bact coli* has been investigated in relation to infective infantile gastro enteritis Bray (1945) first isolated a specific serological type of *Bact coli* from the faeces of babies suffering

Giles C and Sangster G (1948) *J Hyg Camb* 46 1
Gordon J Ingraham M S and Korns R F (1947) *J exp Med* 86 409
Gordon R F and Buxton A (1946) *Vet J* 102 187
Hargreaves E. R. (1947) *Brit med J* 1 720
Hobbs B C. (1948) Personal communication
Hormaeche E. and Peluffo C A (1941) *Puerto Rico J pub Hlth and Trop Med* 17 99
— — and Aleppo P L. (1936) *Arch urug Med* 9 113
Kauffmann F (1944) *Acta path microbiol scand* 21 20
— and Dupont A (1950) *Ibid* 27 552
Keitel H G (1950) *J infect Dis* 86 219
Kirby A C Hall E. G and Coackley W (1950) *Lancet* 2 201
Knipschildt H E (1945) *Undersogelsen over Coligruppens Serologi med saerligt Henblik paa Kapselformerne* Copenhagen Burck
Light J S and Hodes, H L. (1943) *Amer J publ Hlth* 33 1451
— — (1949) *J exp Med* 90 113
McClung L. S (1945) *J Bact* 50 229
Magnusson J H Laurell C and Frisell E (1949) *Svenska Lakartidn* 46 2533
Moore B (1948) *Mon Bull Min Hlth and Pub Hlth Lab Ser* 7 136
Neter E (1950) *Am J Pub Hlth* 40 929
— and Shumway C N (1950) *Proc Soc exp Biol N Y* 75 504
Oakley C L. (1949) *Brit med J* 1 269
Osler A G Buchbinder L. and Steffen G I (1948) *Proc Soc exp Biol N Y* 67 456
Reimann H A Price A H and Hodge J H (1945) *Ibid* 59 8
Report (1946) *Med Res Coun Special Report Series No* 260
Report (1950) Food Poisoning in England and Wales 1949 *Mon Bull Min Hlth and Pub Hlth Lab Ser* 9 254
Scott H Harold (1934) *Some Notable Epidemics* London Arnold.
Scott W M (1933) *Bull int Hyg publ* 25 828
Sevitt S (1945) *J Hyg Camb* 44 37
Smith J (1949) *Ibid* 47 221
Stevenson J S (1950) *Brit med J* 2 195
Taylor J (1951) *Brit med Bull* 7 163
— Powell B W and Wright J (1949) *Brit med J* 2 117
Vahlne G (1945) *Acta path microbiol scand Suppl* 62.
Varela G and Olarte J (1943) *Bull Hyg* 18 505
Watt, J (1945) *Publ Hlth Rep Wash* 60 835
White P B (1926) *Med Res Coun Special Report Series No* 103
Williams G C Swift S Vollum R. L. and Wilson G S (1946) *Mon Bull Min Hlth and Pub Hlth Lab Ser* 5 17
Williams Smith H (1948) *J comp Path* 58 179
Wilson J E (1945) *Vet Rec* 57 411
— (1950) *Ibid* 62 449
Zeissler J and Rassfeld Sternberg L (1949) *Brit med J* 1 267

It has been suggested that this disease may be of virus origin Reimann and others (1945) investigating an outbreak of gastro enteritis with faucial involvement in adults found that bacteria free filtrates of faeces from patients when inhaled by human volunteers were able to cause symptoms of the natural disease Gordon and others (1947) working on similar lines were unable to repeat these results but found that the ingestion by mouth of similar filtrates reproduced the disease It is tentatively accepted that the presence of cold agglutinins and streptococci M G agglutinins in a patient s serum during the convalescent period indicates that the disease is of virus aetiology Keitel (1950) investigating an outbreak of diarrhoea affecting both adults and babies in a transit camp found the serum of the latter in many instances had raised cold agglutinin and streptococci M G titres suggesting a virus infection A similar symptomatology has been noted by Cook and others (1947) and it seems probable that both in the British Isles and in United States of America a type of diarrhoea and vomiting which may affect both babies and adults can occur

Light and Hodes (1943 1949) investigated material from 4 outbreaks of neonatal diarrhoea They were able to isolate a filtrable agent which caused scouring in calves Cummings (1947) working on similar lines obtained the same results but the agent was lost after the fourth passage in calves At present these results must be accepted with caution as calves are so very susceptible to spontaneous diarrhoea There is reasonable evidence that some outbreaks of gastro-enteritis among adults may be caused by virus infection and some evidence that a virus infection may cause disease in babies

In conclusion it may be said that new knowledge on the infections of the gastro intestinal tract has resulted from new methods used in the isolation and identification of organisms and virus Investigations are hampered by the fact that for many infective agents proved to cause disease in man no susceptible laboratory animal is known Our knowledge will continue to advance as the result of close collaboration between clinician and laboratory as both are essential in the proof of disease processes

REFERENCES

Allison V D (1949) *Proc R Soc Med* 42 216
Beckerman F and Laas (1946) *Arztliche Wschr* 1 329
Beeuwkes H Gijsberti Hodenpijl A K A and Ten Seldam R E J (1949) *Maandschr Kindergeneesk* 17 195
Borman E K Stuart C A and Wheeler K M (1944) *J Bact* 48 361
Bray J (1945) *J Path Bact* 57 239
Bruner D W Edwards P R and Hopson A S (1949) *J infect Dis* 85 290
Buchbinder L Osler A G and Steffen G L (1948) *Publ Hlth Rep Wash* 63 1 9
Cook G T and Marmion B P (1947) *Brit med J* 2 446
Cummings G D (1947) *J Paed* 30 706
Denys J (1894) *Bull Acad roy Med Belg* 8 496
Dolman C E Wilson R J and Cockroft W H (1936) *Canad publ Hlth J* 27 489
Dudgeon L S Wordley E and Bawtree F (1921) *J Hyg Camb* 20 123
— — — (1922) *Ibid* 21 168
Edwards P R West M G and Bruner D W (1948a) *Jentucky Agri Expert Sta Bull No* 499
— — — (1948b) *J Bact* 55 711
Field H I (1948) *Vet J* 104 251

making an incision into a cancer of the breast in order to obtain material for section because in the case of rectal cancer the fragment is taken only from the surface of the tumour without injury to surrounding tissues Biopsy is of special value when the diagnosis is obscure but even when there appears to be no element of doubt a confirmation of the clinical opinion is often welcome and there is ample time for a report on the sections before the operation of excision is under taken

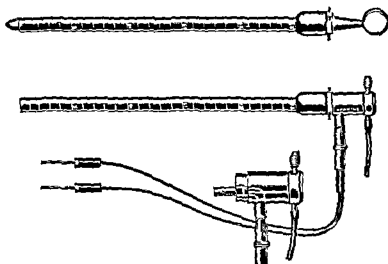


Fig 222 —Small calibre sigmoidoscope 14 millimetres diameter 25 centimetres length Lloyd Davies pattern.

Biopsy is of value also for the diagnosis of lesions which clinically resemble malignant tumours but which actually are not so These include inflammatory lesions cysts unusual types of benign tumours and lesions due to injections of haemorrhoids with unabsorbable oils In these and in many other cases in which there is an element of uncertainty about the clinical diagnosis the microscopical examination of a fragment removed may provide information of the utmost value

Biopsy diagnosis of malignancy

In rectal tumours as in all other neoplasms the histological diagnosis of malig nancy depends on two factors (a) on the atypical appearance of tumour cells and (b) on evidence of invasion or infiltration Both these features may be obvious at once in sections of biopsy fragments because adjoining normal mucous membrane and submucosa are so often removed with the tumour fragment The sharp con trast between malignant and normal tissue then is striking (Fig 224) Even when no normal submucosa happens to have been included the recognition of malignancy is quite easy if the biopsy has been taken deep enough to show spread into the submucosa or muscle (Fig 225) or if it happens to reveal tumour cells within a small vein or lymphatic (Fig 226) There can be no doubt about the diagno is in

CHAPTER 27

RECTAL AND COLON TUMOURS

O V LLOYD DAVIES AND CUTHBERT DUKES

DIAGNOSIS

Sigmoidoscopy

SINCE bleeding per rectum is the first symptom in 80 per cent of patients suffering from cancer of the rectum all cases should be fully investigated by palpation proctoscopy sigmoidoscopy and where necessary by a barium enema examination The introduction of sigmoidoscopes of small calibre (Fig 222) has facilitated sigmoidoscopic examination

First the patients suffer less discomfort secondly a semi loaded bowel can be examined provided the motions are formed and thirdly the recto sigmoid area which is often narrower than the remainder of the bowel can be negotiated with greater ease It is important to observe this area particularly since the radiologist has greater difficulty in diagnosing lesions in this part than elsewhere in the colon The reason for this is the normal narrowing of this area and the fact that the sigmoid loop frequently overlies it

Sigmoidoscopic examination should be carried out in the first instance without any bowel preparation The valuable evidence of a fleck of blood and mucus seen in the lower sigmoid colon will be destroyed if the bowel is prepared but when such evidence is obtained a sigmoidoscopic examination should be carried out after preparation using a larger bore and longer instrument under anaesthesia if necessary Even in the absence of diagnostic radiological confirmation constant sigmoidoscopic findings of blood and mucus in the sigmoid colon warrant a laparotomy There is also a general feeling that in cases of doubt the occult blood test should be used more frequently

Biopsy

In diseases of the rectum and lower pelvic colon biopsy is best carried out by the use of long forceps of the Brunings or St Mark s Hospital pattern by means of which fragments can be obtained from lesions at any height that can be reached by a sigmoidoscope From a lesion in the ano rectal region biopsy material can be obtained through a proctoscope using a smaller instrument of the nasal punch forceps type The technique of rectal biopsy has been well described by Gabriel and others (1951) and by Gabriel (1931) who was one of the first to advocate the routine use of this method of examination Fig 223 shows a low power view of an average catch with biopsy forceps in a case of carcinoma Experience has shown that there is no danger of spreading the disease as there might be for example in



FIG 225—Rectal carcinoma invading submucosa Normal mucosa above (glands cut obliquely) Submucosa below infiltrated with adenocarcinoma A small lymphoid follicle is present deep in the mucosa × 70



FIG 226—Lymphatic permeation by rectal cancer Biopsy from anaplastic rectal carcinoma showing lymphatic permeation in submucosa × 140



FIG 223 —Low power view of biopsy fragments average catch The fragments above and to the left and below and to the right both include submucosa infiltrated by carcinoma and partially cover d by normal mucous membrane The other fragments consist almost en ~y of tumour tissue from the surface × 5



FIG 224 —Biopsy section through edge of rectal carcinoma to illustrate contrast between malignant tissue and normal The clumps of carcinoma cells on the left are infiltrating the submucosa In the normal tissue to the right the glands have been cut transversely × 20



FIG 227.—Pre in vasive carcinoma. Above and to the left a small focus of carcinoma below and to the right normal rectal mucosa with *glands cut transversely* If this is all that is found the pathologist should report "carcinoma in pre invasive phase" and state also whether or not ample free margin was present above and on each side × 100



FIG 228.—Mucus secreting adenoma Most of the epithelial cells which line the glands are distended with mucus and there is very little evidence of epithelial proliferation. × 100

these cases because it rests on both the malignant appearance of the tumour cells and also their invasive behaviour

The interpretation of a biopsy is much more difficult if the pieces are all small consisting of only minute fragments of the tumour without any surrounding tissues It is difficult also in the pre invasive stage of a malignant growth when all the microscope reveals is a localized proliferation of malignant looking epithelium still confined to the mucosa (Fig 227) Whether or not a histological diagnosis of malignancy can be made from a biopsy section which shows no evidence of infiltration depends a good deal on the histological variety of the malignant tumour It would be dangerous to do so in a very small biopsy from a low grade adeno carcinoma if no evidence of invasiveness could be found because the individual tumour cells of a low grade adenocarcinoma closely resemble those of a rapidly proliferating yet non malignant adenoma On the other hand a confident diagnosis of malignancy can often be made without confirmatory evidence of infiltration in biopsies of colloid carcinoma and very anaplastic adenocarcinomas of a high grade of malignancy Even in small biopsies from the surface of these growths malignancy is generally unmistakable

The frequency with which a biopsy diagnosis proves to be right or wrong" does not depend only on the judgment or experience of the pathologist who examines the sections It depends also to a greater extent than is usually appreciated on the skill of the surgeon Although the taking of a biopsy is not a difficult procedure if the right instruments are used yet none the less experience is necessary to obtain satisfactory bits

Biopsy for the diagnosis of non malignant lesions

Most rectal biopsies are undertaken for the diagnosis of lesions suspected of being malignant but biopsy may also be made for the diagnosis of non malignant lesions such as non malignant tumours inflammatory or infective conditions and malformations and reparative processes

Some non malignant tumours such as villous papillomas and pedunculated adenomas are easily recognized by sigmoidoscopic examination and equally easily recognized by biopsy (Figs 228 and 229) but the gross characters of other non malignant tumours are not so distinctive and it may not be possible to diagnose them without biopsy This applies particularly to lymphomas fibromas myomas and lipomas These all appear as firm rounded tumours situated first within the wall of the bowel but later tending to become pedunculated Carcinoid tumours of the rectum have a similar appearance in their early stages of development

Localized inflammatory and infective lesions may give rise to swellings and ulcerations which resemble malignant tumours but most of these are readily distinguished by biopsy In the rectum the commonest of these lesions in Great Britain is the so-called non specific granuloma consisting of a mass of well organized granulation tissue only (Fig 230) Amoebic dysentery and bilharzia may give rise to similar granulomatous tumours In the anal canal tuberculous ulcers and primary chancres may cause lesions which resemble the early stages of epithelioma

Submucous glandular cysts are met with occasionally in the rectum and may be diagnosed by biopsy Some are probably congenital malformations and others traumatic in origin Extensive leucoplakia of the rectum in which the mucosa is



FIG 231 —Paraffinoma of rectum Tumour caused by injection of non-absorbable oil for treatment of haemorrhoids Note larg round spaces in submucosa. These were filled with oil ×40



FIG 232.—Adenocarcinoma of low-grade malignancy invading submucosa of rectum Note regular tubular pattern of glands lined by well-differentiated cells ×116



FIG 229 —Mucus secreting papilloma Villous papilloma of rectum showing villi covered with mucus secreting epithelium × 40

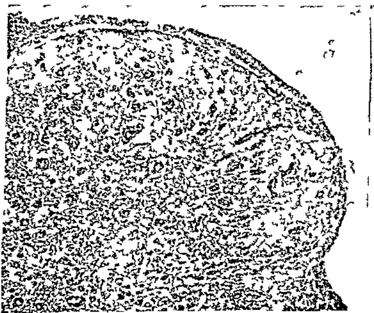


FIG 230 —Biopsy from a rectal granuloma which on sigmoidoscopic examination resembled a carcinoma × 40

in small clusters or they may be arranged in a solid trabecular or alveola pattern It may be difficult to decide whether such a growth is a sarcoma or carcinoma but some part of the tumour generally has features characteristic of carcinoma (Fig 236) These tumours are of a high grade of malignancy metastasize early and have the worst prognosis of all Fortunately this group is the smallest constituting only 2 per cent of all cases of rectal cancer

When comparisons have been made between the histology and the extent of



Fig 233 —Adenocarcinoma of average grade of malignancy invading submucosa of rectum The glandular pattern is irregular and the tubular spaces are lined by closely packed columnar cells with hyperchromatic nuclei 180

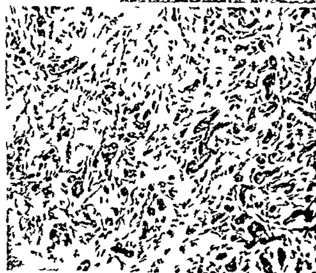


Fig 234 —Adenocarcinoma of high grade malignancy invading submucosa of rectum The darkly staining clusters of carcinoma cells show no obvious glandular arrangement and vary greatly in size and shape × 210

replaced with thick nodules of keratinizing squamous epithelium has been mistaken for a carcinoma Fibroid polyps of the anal canal have a characteristic structure consisting of a central core of dense connective tissue and blood vessels covered with hyperplastic squamous epithelium The injection of non absorbable oil for the treatment of haemorrhoids has been known to cause the formation of a tumour known as a paraffinoma This also may be easily recognized by biopsy (Fig 231)

The taking of biopsies from rectal and anal lesions has been a routine procedure at St Mark s Hospital for 20 years and during this period well over 4 000 biopsy sections have been examined in the pathology department In more than half these cases the biopsy was followed by surgical removal of the tumour or other lesion giving an opportunity for checking the biopsy diagnosis This experience has proved the general reliability and usefulness of biopsy in rectal and anal lesions It often provides information which could not be obtained in any other way

THE RELATIONSHIP OF HISTOLOGY TO SPREAD IN RECTAL CANCER

Cases of rectal cancer treated by radical excision can be divided into four groups according to the extent or spread of the disease as revealed by the examination of the operation specimen In the first or initial stage the growth is limited to the bowel the patient at this stage being described as an A case The second stage is reached when the malignant tumour has spread by direct continuity into adjoining structures but had not yet given rise to lymphatic metastases At this stage the patient is described as a B case The third stage is reached when the malignant growth has spread still further giving rise to lymphatic metastases Patients at this stage are known as C cases If the malignant growth has spread to distant organs such as the liver this is described as the fourth stage

Let us now consider whether any relationship can be traced between the extent of spread of a rectal cancer and its histology The three main histological varieties of rectal cancer are adenocarcinoma colloid (or mucinous) carcinoma and an undifferentiated variety called anaplastic carcinoma simplex

Adenocarcinoma is much the commonest variety constituting 85 per cent of all cases Its histological characteristics are well known and it is sufficient to point out that though the growth usually shows a tubular or acinar pattern there is as a rule very little evidence of mucous secretion either in the cells or glandular spaces Since adenocarcinoma is such a large group it is useful to subdivide it according to the degree of differentiation of the tumour cells into three groups (1) low grade of malignancy (2) average grade and (3) high grade of malignancy (Figs 232–234)

Colloid or mucous secreting carcinoma is the second commonest variety of rectal cancer constituting 13 per cent of cases It has a similar basic structure to adenocarcinoma but differs in that a large quantity of mucus is secreted (Fig 235) When the mucus is stored in individual cells these have a signet ring appearance but if the secretion is extracellular tumour cells may be relatively few in numbers being seen only floating in lakes of colloid or scattered round the margin

The term carcinoma simplex is used to describe an anaplastic type of carcinoma composed of polygonal or spheroidal cells destitute of any glandular arrangement and not showing mucous secretion The tumour cells are scattered about singly or

This is evidence that colloid carcinoma spreads more rapidly than adenocarcinoma and that carcinoma simplex spreads even more rapidly than colloid carcinoma

It is worth pointing out that the conclusion reached with regard to the bad progno is of colloid carcinoma is rather paradoxical and unexpected It might have been supposed that a tumour which secretes mucus would grow more slowly than one which appears to have lost this function and devoted itself exclusively to reproduction This may be because the mucus or colloid material tends to ooze along and distend tissue spaces and lymphatic channels thereby facilitating the spread of neoplastic cells In other words the colloid acts as a lubricant It is certainly true that small quantities of colloid material are sometimes found in lymphatic glands which do not contain neoplastic cells suggesting that this has made its way along in advance

The relationship between histology and spread of tumours is easier to study in some organs of the body than in others There are many reasons for this In the first place it is obvious that such relationship between histology and spread can only be established if the histological varieties are clearly distinct as definitely different let us say as adenocarcinoma colloid carcinoma and carcinoma simplex of the intestine This is seldom the case Another handicap arises from the fact that in some organs of the body the injury caused by a malignant growth is much more attributable to the anatomical position than to any niceties of histology This is particularly true of tumours of the kidney ureter and bladder Then again in some organs of the body the path of local and lymphatic spread of carcinoma is variable or difficult to follow So it is not to be expected that conclusions drawn from the study of intestinal cancer can be extended as easily to other organs None the less it is probably true that each histological variety of cancer has its characteristic tempo of spread even though the pathologist is seldom able to express it precisely

OPERATIVE TREATMENT FOR CANCER OF THE RECTUM

The synchronous combined method of excision of the rectum adopted by most of the surgeons at St Mark s Hospital since 1938 is gaining increasing popularity A full description of the operation is available in everal works For this operation the patient is placed in the lithotomy Trendelenburg position (Lloyd Davies 1939) using special leg supports which allow the abdominal and perineal fields to be adequately exposed so that two surgeons can work at the same time with no inconvenience to either of them (Fig 237 (*a* and *b*))

There are many advantages n this method First no turning of the patient is required during the operation Secondly there is a saving of time and on this account the operation is ideal for the training of young surgeons Thirdly extensive and fixed growths which would otherwise be regarded as inoperable can be removed by this method The fixity of rectal cancers is not always due to extension of the growth but to surrounding inflammation and the late results after excision in these cases is often encouraging

Since the adoption of this operation at St Mark s Hospital the resectability rate has risen from 66 per cent to well over 90 per cent and although no figures are available it is well known that the resectability rate has improved in all centres where this method is u ed

spread in rectal cancer it has been found that different histological varieties behave very differently both in rate of growth and liability to metastasize Thus on the average lymphatic metastases occur in only 50 per cent of cases of adenocarcinoma but are found in 70 per cent of colloid carcinoma and 82 per cent of anaplastic carcinoma simplex The number of lymphatic metastases has also been found to vary with the histology of the growth the average number of metastases in adenocarcinoma being 4 in colloid carcinoma 6 and in carcinoma simplex 8

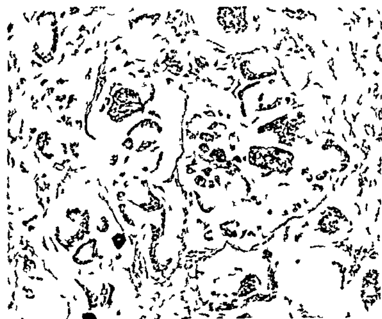


FIG 235 —Colloid carcinoma high grade malignancy Clumps of undifferentiated carcinoma cells are seen floating in collections of mucoid material A few isolated signet cells also present × 100

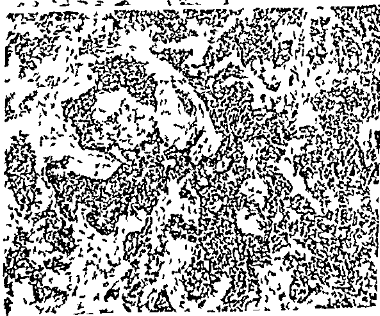


FIG 236 —Anaplastic carcinoma simplex invading rectal submucosa The growth consists of solid clusters and strands of small spheroidal and polygonal cells destitute of any glandular arrangement × 140

cancer were treated by combined excision with 157 operation deaths an overall operative mortality rate of 10 6 per cent but it is easy to show by comparing the figures for different periods that the operative mortality has now declined to less than half what it was 20 years ago (*see* Table below) In 1933–39 it was 17 8 per cent from 1947–50 it was only 7 5 per cent

OPERATIVE MORTALITY FOR COMBINED EXCISIONS AT ST MARK S

Period	*No of cases*	*Operation deaths*	*Mortality rate*
1933–39 – –	281	50	17 8
1940–43 – –	303	31	10·2
1944–46 – –	352	35	10 0
1947–50 – –	545	41	7 5
TOTAL	1 481	157	10 6

It should be remembered that during the second half of the total period shown the resectability rate has risen by nearly 30 per cent The figures of recent years also include an increased number of palliative operations that is combined excision operations performed chiefly for patients with liver secondaries Where the liver is not grossly enlarged by metastases and there is a reasonable amount of normal liver substance the primary growth should be removed The miserable state of pelvic pain constant rectal discharge and tenesmus is thus avoided

The improvement in the operative mortality rate has resulted from many factors and of these the following should be mentioned

First the more careful attention that is being given to pre operative preparation and post-operative care coupled with the better understanding of the fluid and electrolyte balance of the patient (Avery Jones and Morgan 1939) Secondly the more readily available supplies of stored blood for transfusion Thirdly the advent of the sulphonamides and antibiotics have to a great extent minimized the dangers of post-operative pulmonary urinary and abdominal infection Fourthly in the group of cases (3 per cent) who developed small gut obstructions after these operations the use of tubes of the Miller Abbott or Cantor type have been of great service either by way of relieving such obstructions completely or by enabling a further operation to be postponed until the patient s general state is improved by attention to the disturbed fluid and electrolyte balance Finally modern improvements in anaesthesia and early ambulation have also played a part

Position of the terminal colostomy

Since Miles first description of the abdomino perineal method of combined excision the iliac portion of the colon has been brought outside through an incision in the left iliac fossa as a terminal colostomy At a later date Rankin (1927) advised closure of the peritoneal space lateral to the emerging colon to avoid small gut obstruction From time to time this well established position has been departed from and terminal colostomies have been made through or near to the paramedian laparotomy incision It was thought that the intraperitoneal space to the outer side of a colostomy so placed would be too wide for the small intestine to become

The lithotomy Trendelenburg position is advantageous to a surgeon working alone either when performing a combined excision or for the whole range of pelvic operations on the bowel More recently Howkins (1951) has described the use of this position for carrying out extended Wertheim operations

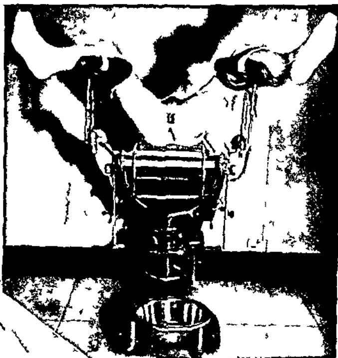
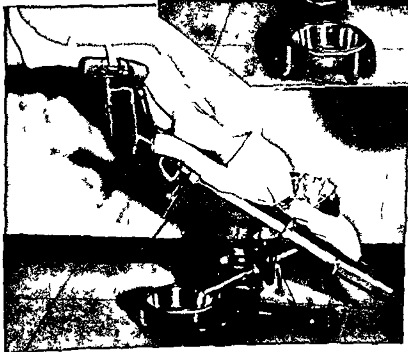


FIG 237—(a) Perineal view of lithotomy Trendelenburg position—the coccyx is marked by a dark triangle (b) patient in lithotomy Trendelenburg position showing special leg supports and sacral rest

(a)



(b)

Operative mortality rate

During the period 1933-50 the operative mortality rate at St Mark's Hospital decreased in a striking way During this period of 18 years 1 481 cases of rectal

Downward lymphatic and venous spread in tumours of upper third rectum and recto sigmoid region

Downward spread by lymphatics or veins is found in approximately 4 per cent of all cases In most of these however the spread had extended only an inch or two In only 2 per cent of cases was downward spread found beyond two inches below the lower margin of the primary tumour Most of the cases showing downward spread were tumours of a high grade of malignancy which might have been detected by biopsy

Peritoneal spread in tumours of upper third rectum and recto-sigmoid

Demonstrable spread in 7 per cent of all operation specimens Most frequent in growths which had spread by direct continuity to peritoneum causing puckering of peritoneum

More commonly found in growths of recto sigmoid than in upper third of rectum Such cases always have a bad prognosis

First and foremost these operations should aim to be as radical as a combined excision and therefore a very careful selection of cases is necessary Secondly bowel function must be good For good function the sensitive anal canal lining the sphincter and levator muscles and the lowest portion of rectum must be retained In a combined excision these structures are widely removed

It is clinically impossible to assess the exact extent of the spread of any rectal carcinoma and since it has been shown that the survival rate after combined excision for C cases (Stage III) in the lower third is so much worse than for cases elsewhere in the rectum growths in this situation should continue to be dealt with by combined excision which is the only operation that attempts to deal with the suspected downward and lateral spread

As already stated some downward spread occurs in 4 per cent of all cases To be radical it is therefore necessary to remove at least two inches of the bowel and its mesentery below the lower border of the tumour Hence no growth in the lower half of the rectum is suitable for a restorative operation From a practical point of view only those tumours out of reach of the finger above 10 centimetres on sigmoidoscopy and above the peritoneal reflection should be considered possibly suitable for these operations Although about half the growths in the rectum fall into this group other considerations must be taken into account.

Tumours found on biopsy to be of a high grade of malignancy should be excluded in view of their greater tendency towards downward spread Extensive bulky tumours filling the pelvis (frozen pelvis) must of necessity be excluded and cases with a short, fat mesocolon or with extensive associated diverticulosis will also be unsuitable

The risks of infection following these operations has been largely eliminated The mortality rate of 7 4 per cent (Lloyd Davies 1950) has meant that a large proportion of cases survive to be followed up and the danger of local recurrence is being appreciated

Careful selection and a radical removal will considerably reduce this incidence but a further factor has also to be excluded namely that of suture line implantation Carcinoma cells are being continually extruded from the surface of the tumour and it is now well established that these cells can continue to grow in any wound or

involved by obstruction A recent review of 1 300 cases of combined excision (Goligher, Lloyd Davies and Robertson 1951) has shown that there is a definite incidence of small gut obstructions through this wider outer space and that even when the space is closed by suturing the colon to the parietal peritoneum from the paracolic gutter to the colostomy site the projecting leaf of mesocolon can give rise to further obstructive troubles

The establishment of a terminal colostomy in the left iliac fossa with closure of the small lateral space still appears to be the best method

Brunschigg's operation

This operation is intended for advanced cases in which the bladder is involved The aim of the operation is to remove all the pelvic organs together with internal iliac and obturator fossa groups of glands The lithotomy Trendelenburg position facilitates the operation considerably and ligation of both interior iliac arteries diminishes the blood loss It is rarely possible to find sufficient peritoneum to form a pelvic peritoneal floor and the small intestine fills the bare pelvis Especial care must therefore be taken to suture the perineal skin accurately and to avoid pressure necrosis of the perineal incision by nursing the patient on alternate sides

Both ureters are transplanted into the mobilized upper sigmoid colon and about three inches of viable colon are made to protrude through the abdominal wall in order to form a spout A split skin graft applied to the protruding colostomy helps to make the spout more rigid and prevents trauma to the bowel The colostomy is referred to as a wet colostomy and a suitable collecting bag has to be worn The value of this operation not only from the point of view of the late results but also from the disability of a wet colostomy has yet to be assessed

Restorative operations

The whole field of restorative operations has been reopened with the advent of the sulphonamides and antibiotics and the consequent reduction in the risk of infection which had previously been a serious bar As is often the case in similar circumstances, the pendulum swings too far With growing experience and the clearer picture of the spread of cancer of the rectum obtained by more accurate examination of operation specimens as shown in the following summary reasonably sound criteria for these operations can now be given

Comparison of five year survival rate after combined excision (1938–43)

All cases—Results more than 10 per cent worse in growths situated in lower third of rectum

Cases with metastases only—Results definitely considerably worse in growths in lower third of rectum Five year survival rate of C cases in lower third only half that of cases in other parts of rectum

Cases without metastases—No significant difference in five year survival rate of growths situated in lower third ampulla upper third and recto sigmoid

General conclusion—The worst place to have a C R is in the lower third This is probably due to possibility of spread by downward and by lateral lymphatics and veins to regions which cannot be removed by radical excision

completed and the patient's general condition is satisfactory For poor risk cases a caecostomy of the invaginating type performed under local anaesthesia is advisable Adequate decompression can be obtained by this method if the caecum is irrigated frequently

Recent advances in colon surgery as also with rectal surgery have been mainly concerned with greater perfection of the pre operative and post operative care of the patient and special preparation of the bowel with sterilizing agents

Intraperitoneal anastomosis is becoming increasingly safe and more popular since the length of hospitalization is much less and the inconvenience of a temporary colostomy avoided by this method

It is often contended that the Paul Mikulicz type of operation is less radical but this criticism only applies to pelvic-colon growths For an operation to be more radical in this region the inferior mesenteric trunk itself must be resected from below the left colic branch and an anastomosis made between the descending colon and the upper rectum

Exteriorizing operations still have a place particularly when there is great disparity in size between the bowel proximal and distal to the tumour and especially in the presence of oedema On the now fortunately rare occasions when anaesthetic difficulties occur and when the time spent upon a careful anastomosis might endanger the patient's life a Paul Mikulicz operation is a quick way out of difficulty

Despite the greater safety in colon surgery provided by the use of sulphonamides and antibiotics most surgeons still prefer to drain the site of the anastomosis either retro or intraperitoneally Bacteriological tests made on the flora of the bowel at operation may provide information regarding chemotherapeutic agents most likely to be useful post operatively but scrupulous cleanliness and careful suturing are still very necessary

The problem of recurrence after resections for carcinoma of the colon is more difficult to study than that of carcinoma of the rectum In these days of bolder and more radical surgery it is unlikely that inadequate removal plays much part except in the very advanced case There are two other possibilities First malignant changes may occur in polyps located in the proximal or distal segments of bowel to be anastomosed and secondly seedling carcinoma cells extruded from the growth may be incorporated in the suture line There is a greater likelihood of this occurrence where crushing clamps are used as in aseptic anastomosis methods For these reasons there is an increasing trend towards the performance of an open anastomosis so that the lumen can be cleaned with solutions such as 1 500 perchloride of mercury to destroy any free cells and any polyps dealt with Crushing clamps are not used on the retained bowel

Carcinoma in the right half of the colon presents a somewhat different problem Most surgeons are agreed that a one stage operation is preferable since the adhesions often produced after a preliminary ileo transverse colostomy tend to make the resection operation difficult Where the diagnosis has been made and the operation can be planned preliminary decompression by a Miller Abbott tube is employed when necessary together with correction of fluid balance and anaemia but occasionally the condition is met with as an emergency operation and in a few instances a complicating acute appendicitis has been recorded To make for greater safety some (Lahey and Colcock 1942 Maingot 1945) have advocated a

granulation tissue Special precautions advised to eliminate this factor are that an exclusion clamp be placed across the rectum at least two inches below the lower border of the tumour after dividing the rectal mesentery at the same level The bowel below the clamp is then irrigated through a proctoscope passed through the anus first with sodium bicarbonate solution and then with 1 500 perchloride of mercury It is essential for the patient to be in the lithotomy Trendelenburg position Sufficient long term figures are not yet available of the results of this manoeuvre but the impression gained is that the method is efficient

Since the revival of interest in restorative procedures a large number of different types of older operations have been resuscitated and modified but no entirely new method has been devised Operations of the abdomino anal (Weir Maunsell) type and abdomino sacral type are used regularly in some centres but the general trend is towards the performance of one stage anterior (abdominal) resections end to end anastomosis being performed deep in the pelvis either supra or infra peritoneal

The comparison of the late results of these operations in different centres is often difficult since considerable confusion exists regarding the position of the junction of the pelvic colon and rectum namely the recto sigmoid area An increasing number of surgeons now regard a recto sigmoid growth as one which lies at the sacral promontory and a growth of the upper rectum as one which lies immediately below the promontory The sooner this is generally agreed the better Supporting evidence for the correctness of this view is given by Goligher and Hughes (1951) who state that in the average case rectal sensation commences at 15 centimetres from the anus and this level in most cases is just below the sacral promontory There is considerable variation in the shape and size of the bony pelvis and the pelvic peritoneal floor varies in height (5–10 centimetres from the anus according to Kirklin Dockerty and Waugh) This peritoneal reflection in the average case is an important landmark for the surgeon

The position of each tumour should be assessed with regard to its height from the anus its relation to the recto vesical pouch (pouch of Douglas) and its relation to the promontory of the sacrum and only then will accurate comparisons be obtained

The final word has not yet been said with regard to these operations but the figures of Dixon (67 7 per cent five year survival rate) and d Allaines (50 per cent five year survival rate) are encouraging

OPERATIVE TREATMENT FOR CARCINOMA OF THE COLON

The treatment of lesions of the colon causing acute obstruction is still a subject for debate The diagnosis depends upon the clinical history the interpretation of the plain skiagrams of the abdomen and in lesions low down sigmoidoscopy On the right side a palpable tumour may be felt but it is more frequently obscured by the distension Many of the lesser degrees of obstruction may be temporarily relieved medically by a Miller Abbott tube and the judicial use of small doses of medicinal paraffin and magnesium hydrate whilst the fluid and electrolyte balance is corrected by intravenous therapy For those cases presenting as an emergency it is now generally agreed that a loop colostomy placed well in the right half of the trans verse colon an exclusion operation is the best treatment for left sided lesions This is followed by resection at a later date when bowel preparation has been

and ascending colon may often be found to b. free from polyps but this area has been known to develop polyposis at a later date in cases in which this portion of the bowel has b en left behind at op ration

When polyposis has been diagnosed the ideal treatm nt is an ileo rectal anasto mosis with total removal of the colon and upper part of the rectum in one stage The polypi in the rectum should be fulgarized b fore operation and this may take several weekly sessions to accomplish If about 10 centim tres of rectum are left these patients have full control and 3–4 bowel actions per day It will be necessary to examine the rectum in such cases at yearly intervals and to fulgarize any further polyps that may develop O casional polyps still occur in one of our patients who has now been followed up for 26 years

Where malignant disease has supervened in the rectum total removal of the large bowel with the establishment of an ileostomy will be nece sary except when the carcinoma is situated in the upper third In these latter cases it may be possible to perform a radical removal and an ileo rectal anastomosis as mentioned above

REFERENCES

Avery Jones F and Morgan C N (1939) *Lancet* 2 611
Gabriel W B (1931) *Brit med J* 1 52
— Dukes C E and Bussey H J R (1951) *Brit J Surg* 38 401
Goligher J C Lloyd Davies O V and Robertson C T (1951) *Ibid* 38 467
— and Hughes E S R (1951) *Lancet* 1 543
Howkins J (1951) *Ibid* 1 872,
Jones T E (1943) *Surgery* 14 342
Lakey F H and Colcock B P (1942) *Surg clin N Amer* 22 773
Lloyd Davies O V (1950) *Proc R Soc Med* 43 701
— (1939) *Lancet* 2 74
Maingot R. (1945) *Proc R Soc Med* 38 377
Muir E G (1947) *Ibid* 40 831
Rankin F W (1927) *J Amer med Ass* 89 1961
Wangensteen O (1943) *Surgery* 14 403
Whipple A O (1943) *Ibid* 14 321

right sided Paul Mikulicz operation but the presence of a temporary ileostomy and the delay in final closure are defects which have prevented this method from becoming popular

Decompression is often necessary before or after resection and it is better if at all possible to be prepared for this eventuality Reliance is placed by many on the Miller Abbott tube (Jones Whipple Wangensteen 1943) In resections in the emergency case Muir (1947) has advised drainage of the lower ileal coils by means of a tube with lateral holes which passes from the ileum through the side to side anastomosis and out through the corner of the invaginated end of the transverse colon farthest away from the anastomosis The transverse colon is invaginated around the emerging tube and brought through a stab wound the colon decompressed by gentle suction and gastric suction is also used By these methods most cases can be dealt with by a one stage operation and in only the very severely obstructed cases is a two stage operation necessary

THE PRESENT POSITION OF THE POLYPOSIS RESEARCH AT ST MARK S HOSPITAL

A search through the records of about 3 000 cases of rectal cancer and about 1 000 cases of colon cancer has shown that the incidence of polyposis in the total bulk of large intestine cancer cases is just under one per cent In cases of generalized polyposis treated by excision of the rectum or by colectomy the examination of the operation specimen has revealed simple polyposis only in about a quarter polyposis plus one malignant tumour in about half and polyposis associated with multiple malignancy in about a quarter The familial character of this disease has been obvious in about two thirds of the cases but in the other third the patient was unaware of any other relative similarly affected Thirty one families affected by polyposis are now being kept under observation but in some of these the familial character of the disease has not yet been established for certain In at least 19 families however there is convincing evidence of a family history of polyposis with many deaths from intestinal cancer An analysis of these 19 families shows that at the present time (1950) they include 286 adults who are blood relatives (parental fraternal or first cousins) Amongst these 286 individuals 111 are known to be cases of polyposis (approximately 39 per cent) It is probable that some individuals at present unaffected may subsequently develop the disease and the ultimate incidence of polyposis in these families may eventually be 50 per cent The sex incidence is approximately equal being males 53 and females 58 It is obvious from these 19 pedigrees some of which cover three generations that either parent may transmit the disease that if one parent only suffers from polyposis about half the offspring are affected and that non affected individuals cannot transmit the disease

It is very important that those individuals in these families likely to be affected should be examined at yearly intervals so that surgical steps can be taken at an early stage Sigmoidoscopic examination is usually sufficient since polyps tend to develop first in the rectum and sigmoid colon and later in the upper reaches of the large bowel A barium radiological examination using the air replacement method will be necessary to determine the full extent in a well established case The caecum

Obstructive crises with vomiting sudden abdominal enlargement and constipation occur in about two thirds of the cases in the first 6 months The child becomes dehydrated and weight loss is often extreme The abdomen is tense shiny and resonant These attacks may be relieved spontaneously or require bowel washouts

If the child survives these early precarious days the disease enters a chronic stage Bowel actions are irregular and frequent suppositories enemas or washouts are necessary The upper abdomen becomes permanently enlarged and inflated and the umbilicus is stretched everted and lies apparently nearer the pubis than the ensiform cartilage The ribs become flared and the diaphragm elevated sometimes as high as the third ribs Some faecoliths may be palpable but they are usually masked by the overlying cushion of gas Writhing peristaltic waves course ceaselessly across the abdomen and borborygmi are frequently audible On rectal examination the anus appears normal the anal canal is long and the rectum is empty and not dilated Through the rectal wall large faecaliths may be palpable in the sigmoid colon

Malnutrition varies with the severity of the obstruction and the success of the measures instituted to overcome it Microcytic anaemia occasionally of severe degree and recurrent putrefactive crises occur in the chronic stage

Superimposed upon this state of chronic partial obstruction are frequent acute attacks Some culminate in serious faecal impactions which require skilful repeated bowel irrigations for relief and others are relieved spontaneously

Untreated cases of Hirschsprung s disease rarely reach adult age or even adolescence

The condition probably occurs once in every 20–30 000 live births Recent studies by Bodian Carter and Ward (1951) show there is a familial tendency and the overall chance of a male sibling being affected is about one in five The probability of a sister being involved is as yet undertermined but must be much less

Pathology

Zuelzer and Wilson (1948) Bodian Stephens and Ward (1949) Whitehouse and Kernohan (1949) Swenson Rheinlander and Diamond (1949) have now published similar uniform findings in a considerable number of cases of Hirschsprung s disease

On post mortem examination or at operation the dilated and thickened bowel is pale in colour contains gas and faecal material and the mesentery is long and contains enlarged lymph glands The bowel appears redundant Distal to the enlarged bowel the intestine assumes a more normal or narrow calibre and thickness The transition between enlarged and normal calibre is sudden and funnel shaped and takes place in 60 per cent of cases in the distal sigmoid or rectum and in the remaining 40 per cent at some more proximal point This segment distal to the dilated bowel appears normal to the naked eye and has been regarded as such for many years When it involves only the rectum it is not apparent without dissection in the pelvis If it extends into the recto sigmoid region or more proximally this apparently normal segment is easily seen is normal in colour and thickness and contains no faeces

This segment is the site of the primary pathology On microscopic examination

M T C E t—41

CHAPTER 28

MEGACOLON

F DOUGLAS STEPHENS

INTRODUCTION

SINCE Hirschsprung s description (1887) of the disease which now bears his name attention has been focused on gross enlargement of the colon In the absence of any obvious organic obstruction it was difficult to account for this dilatation It was considered by various workers to be due to a congenital malformation to an obstruction caused by redundancy kinking or volvulus or achalasia of a hypothetical sphincter or to a neurogenic cause such as imbalance in its autonomic nerve supply

In 1946 it was shown radiographically by Ehrenpreis that the megacolon was not congenital but developed during the ensuing few weeks or months Swenson and Bill (1948) found that in 20 cases of typical Hirschsprung s disease the megacolon terminated at some point proximal to the anus and that the intervening bowel was a spastic segment causing partial obstruction They concluded that the megacolon was secondary to the obstruction and that apart from its hyper trophy it functioned normally Their work favoured the obstruction theory disproved the neurogenic hypothesis and dramatically focused attention on the *terminal more innocent looking segment of bowel*

Subsequently a characteristic pathology has been described in this segment and the mystery which has for so long surrounded this disease is now to some extent clarified Swenson and Bill (1948) first successfully applied the pull through type of rectosigmoidectomy operation as the rational procedure in this disease

Megacolon in the absence of an obvious organic obstruction occurs in another group of cases which have in the past been confused with Hirschsprung s disease The clinical pattern is that of simple chronic constipation which progresses to a stage where the rectum and colon dilate to accommodate the large faecal accumulations

HIRSCHSPRUNG S DISEASE

Clinical pattern

Boys are affected approximately 13 times more commonly than girls Con stipation begins often with the retention for several days of the first meconium stools Subsequent bowel actions are irregular and vary in frequency from daily actions to one in *several weeks The stools are small pellets when hard* and thin toothpaste like ribands when soft Large amounts of flatus are passed and gaseous abdominal distension appears early though it may pass unnoticed at first

can be seen bulging the flanks and raising one or both sides of the diaphragm

Barium enema examination in the chronic stage of the disease reveals characteristic features It is necessary to introduce small amounts of barium emulsion slowly during the screening in order to avoid obscuring the distal segment by superimposed barium in the dilated bowel Observations in the antero posterior oblique and lateral views will demonstrate the pathological segment when present This segment is of variable length and extends from the anus most commonly to the recto sigmoid or distal sigmoid regions It is normal or narrow in calibre and is seen in some cases to undergo a type of segmentation similar to that seen in the small bowel Proximal to this segment the calibre of the bowel rapidly enlarges in s a funnel like manner to become the typical megacolon (Fig 239) The dilatation is maximal immediately adjacent to the funnel The degree of dilatation and the length of the dilated bowel presumably depend on the degree of obstruction offered by the terminal segment In the dilated bowel faecaliths and fluid levels may be visualized



FIG 239—Barium enema radiograph demonstrating the terminal narrow segment (*By courtesy of Lancet*)

In the newborn period the gaseous distension is more evenly distributed through the bowel and the contrast between the terminal narrow-calibre bowel and the dilated bowel is not easily seen Radiographically at this stage the diagnosis may be impossible and repeated examinations at monthly intervals may be required Ehrenpreis (1946) demonstrated the gradual appearance of the typical megacolon in four newborn children The typical findings took from 18 days to 3½ months to appear

the intramural plexuses of Auerbach and Meissner are found to be lacking in ganglion cells The aganglionic bowel extends from the anus throughout the distal segment and extends for 1–5 centimetres into the funnel shaped transition zone (Fig 238) There is no evidence of inflammatory reaction and the condition is regarded as a congenital aplasia of the ganglion cells Abnormally large non medulated nerve bundles are seen in the sites of the intramural plexuses The origin of the nerve fibres has not been established Both the absence of ganglia and the presence of those nerve bundles are abnormal features and are characteristic of Hirschsprung s disease

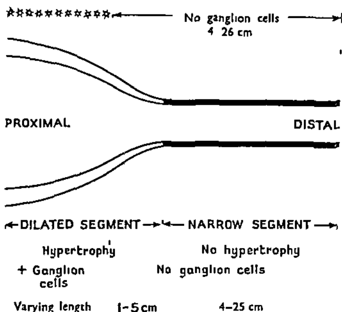


Fig 238 —Pathology of 28 cases of Hirschsprung s disease (*By courtesy of Lancet*)

The dilated segment when examined microscopically is found to consist of hypertrophied muscle coats of the bowel with normally arranged ganglia in the *intramural plexuses*

The functional manifestation of the aplasia is absence of the peristaltic movement in this segment which fails to propel the faecal stream This absence of *peristalsis in the distal segment was demonstrated in eight cases of Hirschsprung s* disease by Swenson Rheinlander and Diamond (1949) in their studies of colonic motility using a multiple balloon technique They showed also that this segment *possessed increased tone*

Radiological appearances

Swenson and Bill (1948) and Neuhauser (1949—quoted by Swenson Rheinlander and Diamond) first described the typical radiological appearances of Hirschsprung s disease They were able to demonstrate a terminal narrow spasmodic segment distal *to the megacolon* in all their cases of Hirschsprung s disease The plain radiographs of the abdomen reveal gaseous distension of the bowel particularly of the colon though in the first few weeks it is more evenly distributed The gas filled gut

To prevent retraction and spilling over of the faeces into the defunctioned segment a Perspex dumb bell rod is inserted under the spur and left *in situ* until after the recto sigmoidectomy operation On the sixth day after the operation the defunctioned segment is washed through and this procedure is repeated daily until the return is clear Up to 3 months is allowed to elapse before the recto sigmoidectomy operation is performed

Recto sigmoidectomy

The preliminary preparation for the recto sigmoidectomy consists of further distal colon irrigation and daily installation of sulphathaladine suspension for five days Systemic penicillin and local instillation is commenced the day prior to operation and streptomycin is given post operatively when indicated An intra venous infusion is commenced prior to operation and changed to blood transfusion as required Intratracheal ether with nitrous oxide when the diathermy is used is a convenient anaesthetic

The child is placed in the combined lithotomy and Trendelenburg position to gain simultaneous access to the abdomen pelvis and perineum For babies under two years the infant s operating frame is very satisfactory (Fig 240)

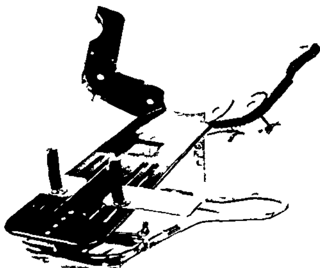


FIG 240—Infant s operating frame (*By courtesy of the Medical Supply Association Ltd*)

The afferent colostomy stoma is occluded with a suture for the duration of the operation and the bladder is drained with a urethral catheter which is retained for 24 hours after the operation

Through a left lower paramedian incision the distal colon can be adequately explored The pale thick walled redundant megacolon in the collapsed state is easily recognized and the site of transition between dilated and narrow bowel is identified If the transition occurs in the pelvis it may not be seen until after the bowel is dissected from its peritoneal covering in which case reliance must be placed on the positive radiological diagnosis

Treatment

In the past the reports on the various forms of treatment for Hirschsprung s disease have been conflicting This was due presumably to the confusion caused by using the term megacolon which includes cases of idiopathic chronic constipation as a synonym for Hirschsprung s disease

In a follow up of 39 cases of Hirschsprung s disease by Bodian Stephens and Ward (1949) no cases were cured Eleven of the children had succumbed Various forms of conservative medical treatment had been applied with only temporary if any improvement Spinal anaesthetics and sympathectomy operations caused no more than temporary relief of symptoms Excision of part or whole of the dilated colon was followed by recurrence of all the obstructive phenomena in the bowel proximal to the anastomosis A colostomy performed in the dilated bowel was found to function normally

Swenson and Bill (1948) studied 20 cases of Hirschsprung s disease and from their observations devised an operation called recto sigmoidectomy to remove the terminal spastic segment conserving the megacolon and anastomosing this dilated bowel to the anus with preservation of the sphincter mechanism

The pull through recto sigmoidectomy operation described below embodies the principles suggested by Swenson and others (1948 1949 1950) but varies in some points in technique

The procedure is staged into a preliminary defunctioning transverse colostomy followed when the general health of the child is optimal by the recto sigmoidectomy operation and then closure of the colostomy

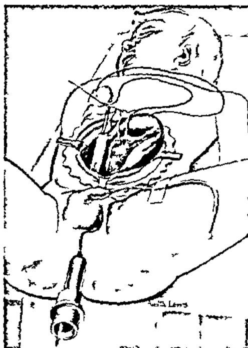
Colostomy

The colon is first emptied by bowel washouts These are repeated daily for about a week Hard faecaliths which necessitate manual disintegration under anaesthesia may become apparent after removal of the faecal mud and gas

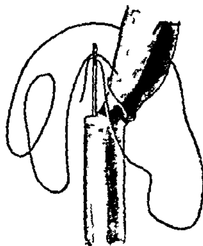
It is usually possible to tide over severe obstructive phases by washouts The passage of the tube through the terminal segment is often more difficult in the obstructive phases because of kinking of the bowel at the transition site and because of compression of the narrow segment by the loaded megacolon which wedges itself in the pelvis The introduction of the tube is facilitated by guidance with the index finger

During the course of washouts the child improves in health the appetite returns and the subject becomes a much better operative risk

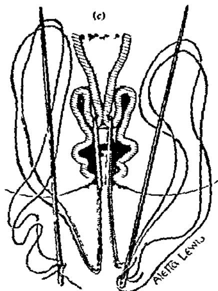
The distal bowel is then explored through a right upper rectus muscle splitting incision and the junction of the dilated and narrow colon is demarcated with two black sutures If the junction is in the pelvis it may not be visible at this operation If any firm faecaliths are found remaining in the colon they are gently disintegrated by direct compression through the bowel wall The distal colon is then defunctioned with a transverse spur colostomy To prevent prolapse in the early and later post operative periods in children whose straining is sometimes uncontrollable the peritoneum is sewn to the thick walled colostomy loop The opening in the abdominal wall is made large enough to admit only the fifth finger through the colostomy stoma The colon is deflated by opening the colostomy at the end of the operation



(a)



(b)



(c)

Fig 242 —A sigmoidoscope is introduced through the anus into the freed bowel This bowel is encircled with two strong braided silk loops which are then loaded on to two 14-inch needles These are passed through the bowel wall into the sigmoidoscope which is then withdrawn Traction on the silk produces a prolapse of the freed segment of intestine into the perineum (*By courtesy of Proceedings of the Royal Society of Medicine*)

It has been found that there is sufficient redundancy of bowel to permit the pull through type of resection of the pathological segment The colic and marginal vessels are long in proportion and adequate in size and length to supply the hyper trophied bowel to its new site

The pathological segment includes all the terminal normal calibre bowel and extends to approximately half way up the cone shaped dilatation The site for resection is therefore at some convenient site proximal to this point depending on the vascular arrangement and the redundancy of the bowel This point is marked with two more black seromuscular sutures

The colic vessels supplying the pathological segment are ligated and divided The arched colic vessels to the hypertrophied bowel and the marginal vessels are examined carefully and if the most distal vessel is too short it must be sacrificed Sufficient length is obtained from the higher colic vessels which are usually arched in the mesentery and lengthen on straightening together with the marginal vessels The superior rectal artery is then doubly ligated with linen and divided at the brim of the pelvis after ensuring the safety of the ureters

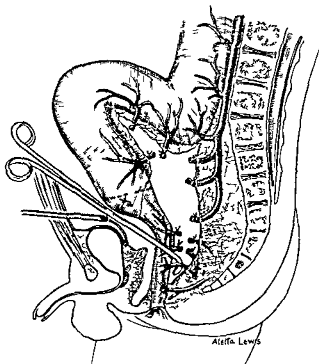


Fig 241 —Diagram showing the freeing of the narrow segment and ligation of its arterial supply (*By courtesy of Proceedings of the Royal Society of Medicine*)

The peritoneum is then divided along the lateral aspect of the narrow segment and then across the front of the rectum deep in the pelvis This bowel and rectum is then cored out of the supporting tissues so as to disturb the remaining pelvis organs and nerves as little as possible The blood vessels entering the rectal wall are under run with right angle forceps and divided with the diathermy on the longitudinal muscle coat

applied on the fourteenth day and formal closure of the colostomy is performed a week or two later

In cases of mild symptomatology Swenson has performed the operation with success in one stage The technique here described does not follow Swenson s original description of the operation in the following points He divides and oversews the bowel within the abdomen and pulls it through subsequently For the anastomosis in the perineum he uses two layers of sutures for the muscle and mucosa

Results following recto-sigmoidectomy

The overall results of this form of surgery are most encouraging in the early follow up extending to 2 years The bowels evacuate spontaneously and without straining Abdominal distension is absent or mild and easily relieved by passage of flatus The older children appear to have an adequate rectal sensation and a normal urge to defaecate

The radiological appearances confirm the clinical observations though the actual diameter of the bowel is still slightly above normal after 12 to 16 months

The rationale of the operation devised by Swenson and Bill for Hirschsprung s disease is confirmed by the follow up results

Complications of the operation

In a series of 37 cases treated at the Hospital for Sick Children Great Ormond Street there were two operative deaths and one post-operative

Three children though not incontinent of faeces soiled themselves for several months two have completely recovered and the third continues to soil One child developed a temporary bladder paralysis which has subsequently recovered com pletely Two developed strictures at the suture line necessitating dilatation for some months

Three cases have recurrence of symptoms one is unable to evacuate spon taneously two have intermittent distension necessitating in one a bowel washout from time to time In these three children too much pathological bowel adjacent to the anus remains and still causes a hold up of the faecal stream

Alterations in the technique designed to overcome these complications are incorporated in the above description of the operation

CHRONIC CONSTIPATION

Clinical pattern

Boys are affected twice as frequently as girls The age of the onset of symptoms varies between the first few months of life and early adolescence the average being approximately 2 years

Although in some cases there is a tendency to constipation in infancy a definite time of onset of the more severe condition can usually be given It followed in some cases a change of feeding from breast milk to cows milk mixtures in infancy or in older children an acute illness such as measles tonsillitis meningitis a cold or diarrhoea Parental neglect a disturbance of the child s normal routine or a defect of the child such as deafness or mental deficiency contributes towards the

The bowel is entirely freed distally as far as the levator ani attachments posteriorly and laterally and to the apex of the prostate anteriorly (*Fig 241*)

The abnormal segment is then intussuscepted through the anus using the sigmoidscope and sling method described by Browne (1949) and illustrated in Fig 242 (*a b* and *c*) (The needles used in this procedure are 14 inches long)

At this stage the peritoneal floor and abdominal wall are reconstituted by the abdominal surgeon

The prolapsed bowel is then washed with antiseptic The outer wall is incised longitudinally to within an inch of the anocutaneous junction and through the opening the inner segment is withdrawn until the demarcating sutures come into view The inner segment is then opened permitting the introduction of the sigmoidoscope to distend its lumen (Fig 243) Four non strangulating equally spaced guide sutures are inserted on heavily curved needles through all coats of both layers of bowel ¼ inch from the anocutaneous junction



Fig 243 —Showing the longitudinal incision of the outer and inner segments of intus suscepted bowel The sigmoidoscope has been re introduced and guide sutures are placed through both segments (*By courtesy of the Annals of the Royal College of Surgeons*)

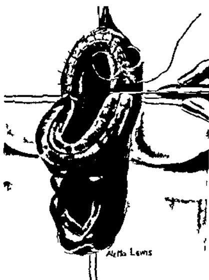


Fig 244 —The cutting of the double layer of bowel by means of a diathermy needle and its sewing by linen vertical sutures inserted with an extra twist to hold the edges of the mucosa together (*By courtesy of the Annals of the Royal College of Surgeons*)

The prolapsed bowel to within ¼ inch of the anocutaneous line is then excised with the diathermy and sutured with interrupted muscle and mucosa apposing linen sutures (Fig 244) The anastomosed bowel is reinserted inside the anus and the guide sutures are left long and protruding from the anus so that the suture line can be retrieved in the event of haemorrhage

On the twelfth post operative day if digital examination of the anastomosed region is satisfactory the Perspex rod is removed The spur crushing clamp is

In the untreated cases some children learn by experience to overcome some of the more irritating symptoms and the cycle may be reversed with a gradual return to normality In others the symptoms persist into adolescence

Good general health is maintained and major abdominal crises other than the colic of intestinal peristalsis are rare

Radiographical appearances

The clinical syndrome chronic constipation faecal overflow and abdominal masses may be present for years in the absence of appreciable radiographical changes If the bowel has not been prepared faecaliths can be seen as filling defects in the rectum (Fig 245) The earliest change on barium enema radiographical examination are a fullness and straightening of the rectum which lacks the normal curves and folds The rectum then later distends the size being limited by the bony walls of the pelvis



Fig 245 —Barium enema showing early appearance of chronic constipation Rectum distended by large faecal mass shown as a filling defect in the barium column

As the distension becomes more apparent and extends proximally into the sigmoid megacolon develops It takes one of two forms

Terminal reservoir type

The rectal distension extends into the distal sigmoid so that the rectal and colonic enlargement is seen as a straight column of barium filling the pelvis and rising to the level of the iliac crests umbilicus or even to the xiphisternum Proximal to this column the bowel assumes its normal dimensions (*see* Fig 246 (*a*)) This resembles the dilatation of the rectum and sigmoid above an anal stenosis

breakdown or failure of development of a regular bowel routine and the appearance of this syndrome

Constipation is the first symptom to appear The motions *become dry* hard and infrequent In the initial stages the passage of large hard motions is painful as evidenced by screaming at stool blood streaks and then holding back of the motion The cycle of constipation *painful defaecation and holding back* leads to a passive loading of the rectum and sigmoid with firm faecal masses and in time to a moderate abdominal enlargement

In the early stages there is *no abdominal enlargement but hard faecal masses* may be palpable along the course of the sigmoid colon When the faecal *accumulation becomes larger the* sigmoid distends and becomes apparent on abdominal *examination Proximal to this some gaseous distension causes* temporary enlargement though rarely to the extent of flaring the rib elevating the diaphragm and averting the umbilicus as occurs in Hirschsprung s disease Peri*staltic waves are rarely visible and borborygmi and flatus are usually infrequent*

When the faecal masses in the rectum become very large and hard the predominant symptom of constipation gives wav to a so called diarrhoea or faecal *incontinence Small amounts of newly formed soft faeces are then continually* massaged by peristalsis to the exterior through the anus by day and night Contamination of clothes hands and face and a constant foul odour are the *inevitable consequence of this stage*

A fear of the pot develops and bribes and coaxing in the use of this receptacle are completely without avail The patient prefers to defaecate in bed or in the standing position but a sense *of shame or embarrassment usually induces the* child to perform the act in solitude Enuresis by night and sometimes by day is frequently an additional burden The child becomes very difficult to manage both at home and at school A psychological problem develops which appears *to be* made worse by punishment and which improves dramatically with the appropriate treatment of the physical condition

Pain of a colicky nature occurs concurrently with drastic and *varied purgation* which is administered by a well meaning parent

On examination the child is usually quite healthy in appearance The abdomen is normal or slightly distended and there is rarely evidence of long standing abdominal enlargement Large and small faecal concretions in the sigmoid colon are usually palpable in the umbilical region and lower abdomen

The perianal region is *in the early stages clean but with the onset of the para*doxical diarrhoea it becomes moist and stained a brownish colour The anal canal is short and the walls of the distended rectum are flattened against the sides of the bony pelvis The rectum is *usually full of firm faeces The rectum remains* cavernous even after thorough evacuation of the faeces

Such conditions as mucosal splits fissures piles and prolapse of the rectal mucosa may be present *These develop secondarily to the straining and disappear* with treatment of the underlying condition

Course

This condition is benign and has a tendency towards gradual improvement over a period of years

These patients can be adequately treated in their homes if the services of a district nurse are available

Although this 5–7 week routine is applicable to most cases a shorter routine may be sufficient in those of recent onset and with little or no rectal or colonic dilatation and a more prolonged course is necessary for cases with greater dilatation

Purgation

Many purgatives have usually been tried with little or no success in the course of this complaint After evacuation of the colon these same purgatives become effective Commence purgation after the rectum and colon have been thoroughly emptied Where the dilatation of the rectum or colon is considerable a mixture containing neostigmine bromide has been found to be effective

Neostigmine bromide – – –	0 154	gr	10	mg
Magnesium sulphate – – –	20	gr	1 2	gm
Petroleum emulsion (50 per cent) –	60	min	4	ml
Water to – – – – – –	120	min	8	ml

Commence with 4–8 millilitres as the first dose and increase gradually until in larger children up to 24 millilitres can be given twice daily For other children where the dilatation is slight ordinary aperients and purgatives are effective

The motions should be kept soft for some months after the bowel washout regime When necessary additional petroleum emulsion should be administered in doses large enough to produce the desired softening effect

Regular bowel habits

Training to a regular bowel regime is implemented at the commencement of treatment For those who suffer from a fear of the pot no exception is made for after the thorough evacuation of the bowels it is quite easy to train them to a routine

Removal of underlying predisposing causes

Assistance and advice in cases of parental mishandling of the child and special prolonged care of backward or deaf children are necessary to ensure that the old habits are forgotten and the new routine is maintained

During any illness which occurs in the course of treatment or in the ensuing few months relapses are liable to occur The motions must be kept soft and regular with an appropriate increase in the aperients or even a temporary resumption of washouts

Results of treatment

After the initial total evacuation by washouts the constipation the paradoxical diarrhoea and the pain on defaecation subside With continued treatment according to the regime outlined above improvement is usually maintained The enuresis in many cases is alleviated fear of the pot and the general irritability are eliminated and the child s appetite and general health improve

Relapses are prone to occur if the predisposing causes persist or if intercurrent illnesses develop during or soon after treatment



(a) (b)

FIG 246 —Barium enema in a case of chronic constipation aged 4 years Terminal reservoir type (b) same case as (a) aged 14½ years showing diminution in calibre of bowel treated by medical measures only

Tubular dilatation of the rectum and sigmoid

The barium column distends the rectum and continues proximally into the tortuous dilated sigmoid

Management

The following regime has proved very satisfactory

Evacuation of rectum and colon

If the rectal content is very hard it is necessary to evacuate it manually under an anaesthetic If soft it can be removed by daily bowel washouts until the rectum is clean and the abdominal masses disappear In 1 2 or 3 days the rectum and colon should be clean

It is found that spontaneous bowel actions commence and the paradoxical diarrhoea ceases after the first few washouts but because at this stage the over distended rectum does not completely empty itself after apparently normal bowel actions further washouts are necessary for a prolonged period to prevent re accumulations Bowel washouts should be performed therefore 3 times a week for 3 weeks and twice a week for 2 weeks Thereafter weekly for several weeks is usually sufficient

It is important that the nurse performs washouts and not enemas for the latter do not ensure a complete evacuation and are ineffective in alleviating the symptoms in the chronic stage

CHAPTER 29

FLUIDS AND ELECTROLYTES IN GASTRO ENTEROLOGY

T D KELLOCK

GASTRO-ENTEROLOGICAL conditions are particularly likely to produce disturbances in water and electrolyte metabolism because not only is the gastro intestinal tract the sole site of absorption of these substances but very large quantities of them are secreted daily into it Clearly therefore an understanding of the way in which these disturbances can arise is essential for their prevention and for their correction when present.

It is proposed here to discuss the essentials of normal electrolyte physiology outline the various ways in which this can be disturbed in gastro-enterological cases review particular diseases in which these disturbances can play a part and offer some suggestions on how such clinical states can be assessed and treated

The normal healthy adult in a temperate climate has a water balance as follows

Intake (millilitres)		*Output (millilitres)*	
Water by mouth –	1,200	Urine – – –	1 200
Water content of food –	1 000	Invisible loss (lungs and skin) – – –	1,200
Water of oxidation –	300	Stools – – –	100
	2,500		2 500

The invisible loss in surgical patients is however greater Fuge and Hogg (1938) showed in 12 cases that it varied from 1 154 to 1 830 millilitres daily according to the size of the patient with an average of 1 457 millilitres

Thus the oral intake and the urinary output are usually about equal and the other factors in this balance are often ignored sometimes with serious consequences

The normal sodium intake which is mostly in the form of sodium chloride is between 3 and 10 grams as NaCl Of this only 1–2 grams are from the salt content of food the balance consisting of salt added in cooking or at the table The loss in the normal stool is about 0 2 gram daily (Coller and Maddock 1940) In the absence of sweating the loss from the skin is negligible (in spite of the large invisible loss of water) and the kidneys excrete the excess

Potassium is the main intracellular cation of the body Recently it has been realized that serious disturbances of potassium balance can occur in alimentary disorders and that a potassium deficit can be induced by the replacement of intracellular potassium by sodium The normal intake of potassium depends

Although a rapid symptomatic cure frequently occurs the dilatation of the rectum and colon takes longer to subside (*see* Fig 246 (*a*) and (*b*))

I wish to thank the physicians and surgeons of the Hospital for Sick Children for their help and co operation in the management of these cases I am most grateful to Dr Martin Bodian for permission to use his pathological data and to Dr B C H Ward for his co operation in the radiological studies

REFERENCES

Bodian M Stephens F D and Ward B C H (1949) *Lancet* 1 6
— — — (1950) *Ibid* 1 19
— Carter C O and Ward B C H (1951) *Ibid* 1 302
Browne D (1949) *Proc R Soc Med* 42 221
Ehrenpreis Th (1946) *Acta chir scand* 94 *Supp* 112
Hirschsprung H (1887) *J Kinderheilk* 27 1
Swenson O and Bill A H Jun (1948) *Surgery* 24 212
— Neuhauser E B D and Pickett L K (1949) *Pediatrics* 4 201
— Rheinlander H F and Diamond I (1949) *New Engl J Med* 241 551
— (1950) *Surgery* 28 371
Whitehouse F R and Kernohan J W (1949) *Arch intern Med* 82 75
Zuelzer W W and Wilson J L (1948) *Amer J Dis Child* 75 40

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Swenson O and Bill A H Jun (1948) *Surgery* 24 212
— Neuhauser E B D and Pickett L K (1949) *Pediatrics* 4 201
— Rheinlander H F and Diamond I (1949) *New Engl J Med* 241 551
— (1950) *Surgery* 28 371
Whitehouse F R and Kernohan J W (1949) *Arch intern Med* 82 75
Zuelzer W W and Wilson J L (1948) *Amer J Dis Child* 75 40

When it is appreciated that the total plasma volume is only 3 500 millilitres it will be realized how rapidly a serious deficiency can arise if the normal re absorption of the fluids does not take place

The chemical composition of these fluids is given by Randall and his colleagues (1949) as follows (the amounts are in milliequivalents per litre)

Fluid	*Na*	*K*	*Cl*
Gastric – – –	60 4	9 2	84 0
	(9–116)	(0 5 32 5)	(7 8–154 5)
Small bowel – –	111 3	4 6	104 2
	(82 147 9)	(2 3–8 0)	(43–137)
Ileostomy (recent) –	129 4	11 2	116 2
	(105 4 143 7)	(5 9–29 3)	(90 136 4)
Ileo tomy (adapted) –	46	3 0	21 4
Caecostomy – –	52 5	7 9	4 5
Bile – – – –	148 9	4 98	100 6
	(131–164)	(2 6–12)	(89–117 6)
Pancreas – – –	141 1	4 6	76 6
	(113–153)	(2 6–7 4)	(54 1–95 2)
Plasma (Gamble) –	142	5	103

It should be noted that the variation is extremely large Moreover when there is any great loss there is usually a mixture of a number of different juices for example in vomiting there may be loss of gastric juice and also of some regurgitated duodenal contents In general it can be said that fluid lost from the upper part of the intestinal canal tends to contain an excess of chloride and thus to be acid whereas that from the lower part of the bowel contains relatively more bicarbonate and is in consequence alkaline

MODES OF DERANGEMENT OF FLUID AND ELECTROLYTE BALANCE

Clearly a disturbance in the normal constitution of the body fluids can be caused by a number of factors Inadequate intake excessive or unbalanced intake exces sive loss or inadequate excretion can all cause such a disturbance and in the majority of cases it is a combination of these factors that is responsible for the development of clinical syndromes due to such derangements

Excessive intake

This is rare except when parenteral fluids are given because very large oral intake leads to vomiting The commonest error is the administration of excessive sodium The danger of this is in part due to the use of the term normal and physiological saline which has the implication that this is a safe fluid which can be given with impunity It must be remembered that the normal intake of sodium chloride is 3–10 grams daily and that each litre of normal saline contains 9 grams Consequently any amount greater than one litre contains more than the normal daily intake

Excessive potassium intake by itself is extremely unlikely to cause symptoms but in the presence of a diminished urine volume even a moderate intake of potassium may be dangerous

largely on the amount of animal protein ingested and on a low protein diet is approximately 2 0 grams daily (Leaf and Camara 1949) The major portion of this is excreted in the urine

Renal control

In healthy individuals the kidneys maintain an extremely efficient control over the fluid and electrolytes of the body excreting excess and conserving whatever may be needed for normal function Unfortunately the efficiency of the kidney may be gravely impaired in many diseases Dehydration or shock may reduce the glomerular filtration rate and any serious illness may diminish the re absorptive capacity of the tubules Moreover there are limits to the capacity of even a healthy kidney Thus with healthy kidneys the volume of obligate urine (that amount necessary to remove all excess electrolytes and by products of metabolism such as urea) depends on the osmotic pressure of the solutes that have to be removed if the plasma concentration is to be kept normal This may vary from 150 to 900 millilitres if maximum concentration is obtained

Naturally the more the concentrating power of the kidney is impaired the greater is the amount of urine necessary to excrete the same amount of waste products Thus the obligate urine can be calculated from the maximum specific gravity to which the kidneys can concentrate the urine as follows (Coller and Maddock 1940) These are amounts necessary to excrete 35 grams of waste products

Specific gravity	*Obligate urine (millilitres)*
1 032–1 029	483
1 028–1 025	595
1 024–1 020	605
1 019–1 015	850
1 014–1 010	1 439

Moreover it should be noted that while the body is efficient within limits at retaining sodium to compensate for a deficit it shows less ability to conserve potassium in a similar fashion On the other hand even in the presence of gross renal damage it is possible for some kidneys to excrete an excess of potassium by direct tubular excretion (Leaf and Camara 1949)

Gastro intestinal secretions

According to Gamble (1947) the average volumes of the various gastro intestinal juices that are secreted (and normally totally re absorbed) in 24 hours are as follows

Juice	*millilitres*
Saliva	1 500
Gastric juice	2 500
Sucus enterious	3 000
Bile	500
Pancreatic juice	700
TOTAL	8 200

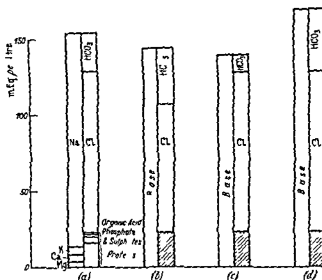


FIG 247 —The normal composition of plasma is shown in (a) The amounts of the various electrolytes are shown in milli equivalents per litre according to the scale In the above diagrams the different cations are not shown separately but are grouped together as total base and the anion other than chloride and bicarbonate are similarly grouped together

(b) Shows the position in pyloric stenosis Here there has been loss of chloride in excess of sodium and potassium although there has been some loss of both these cations Consequently there has been a slight reduction in the total base and a great reduction in the chlorid content Equality of the two columns has been maintained by an increase in the bicarbonate that is an alkalaemia

In (c) there has been a loss of sodium and potassium in excess of chloride as may occur with a duodenal fistula The concentration of total base has fallen and the bicarbonate has been reduced leading to acidaemia

In (d) the administration of alkali has led to an increase in the total base and equality has been maintained by an increase in bicarbonate thus producing an alkalaemia though of a different type to that in pyloric stenosis

Excessive water intake is a less common cause of disturbance than excessive sodium intake but the injudicious use of intravenous dextrose or an excessive intake in the presence of renal damage may occasionally produce symptoms

Diminished excretion

Diminished excretion is of comparatively little importance in gastro enterological cases unless combined with excessive intake However prolonged extrarenal azotaemia as may occur in many of these cases can occasionally produce tubular necrosis and this may lead to a diminished output In the milder and commoner degrees of renal inefficiency however it is more likely that there will be excessive loss of water and electrolytes due to poor concentration of the urine

Excessive loss

Excessive loss is the commonest cause of the disturbances under consideration Vomiting gastric aspiration intestinal fistulae and diarrhoea may lead to the loss of water and electrolytes in very large quantities as can be seen by considering the large amounts normally secreted and re absorbed The type of disturbance produced will be determined by the composition of the fluid lost and the treatment given

Inadequate intake

This is one of the commoner factors in the type of case under discussion Dysphagia from any cause anorexia vomiting or the therapeutic restriction of oral fluids as in post operative cases or after haematemesis will all lead to deficiencies if uncorrected and particularly when combined with an excessive loss

If there is no attempt at administration by other routes there will naturally be a deficiency of water and all electrolytes but the water deficiency will probably be the most important as the invisible loss will continue However there will also be a deficiency of sodium as in order to maintain an isotonic extracellular fluid a hypertonic urine containing large quantities of sodium and chloride will be excreted Potassium loss will also continue *via* the urine

In the majority of cases attempts are made to supplement the inadequate intake by other routes but too often the intake thus achieved is only partly adequate Thus in some cases water alone may be given and the sodium and potassium deficiencies be left uncorrected Marriott (1950) has drawn attention to the danger of treating mixed deficiencies by giving water alone under the impression that the dehydration is only due to a lack of water This danger is now less since the dangers of sodium or salt deficiency are more widely appreciated but frequently the intake of an adequate amount of potassium is not achieved

The following examples will illustrate the various types of deficiency caused by an inadequate intake

In the conservative treatment of haematemesis nothing was given by mouth and this led to deficiency of water sodium and potassium In post operative cases it often happens that the intake is restricted to water only by mouth and nothing else is given by any other route and there is a potential deficiency of sodium and potassium in an even greater number of post operative cases saline solution may be given intravenously and an adequate intake of water and sodium be obtained, but there is still inadequate intake of potassium and other ions

equilibrium is only achieved by a high serum bicarbonate This in turn leads to a high urinary chloride output Thus it is possible to have a normal volume of urine with a normal or raised chloride content in the presence of severe electrolyte disturbance The popular assumption that water and salt balance will be properly maintained if daily urine volume exceeds 1 500 millilitres and urine salt concentration approximates 3 grams per litre may be misleading

Thus in any condition leading to the loss of gastric juice in large amounts there will be a deficit of water chloride sodium and potassium The relative importance of each of these deficits will largely depend on the therapeutic measures that are adopted

Intestinal fistulae

The loss of fluids and electrolytes that can occur through external fistulae in various parts of the gastro intestinal tract or from the bile duct or pancreas is *enormous* as can be *realized by considering the quantity of fluid that is secreted* into the bowel daily In general the higher up the tract the greater will be the loss Thus a duodenal fistula may discharge several litres of fluid daily but the amount will depend on the degree of hydration of the patient

The fluid lost from these fistulae is hypotonic and thus there is a greater loss of water than electrolytes The composition of the fluid varies greatly but in all cases there will be a loss of sodium potassium and chloride and in some cases of bicarbonate In general the electrolyte concentration of these fluids is about two thirds that of the plasma The fallacy however of regarding the sodium and chloride content together as salt that is equal proportions of each is well shown by the case of duodenal fistula described by Denton (1949) In this case the sodium loss was twice that of chloride and in consequence a severe acidosis developed which was not relieved by the administration of sodium chloride but responded to sodium lactate Under these circumstances the body needed to retain the sodium of the administered saline but was receiving an excess of chloride the urine consequently was found to have a high chloride content although the plasma showed hypochloraemia This is thus a second example of circumstances in which it is possible to have a severe electrolyte disturbance with hypochloraemia in the presence of a urine of adequate volume and chloride content

Potassium deficiency also occurs in such cases and has been described by Smith (1950) in a case of biliary fistula in which the serum potassium fell to 0 8 mEq per litre Evans (1950) gives details of a case of faecal fistula in which the serum potassium remained between 1 and 2 mEq per litre in spite of therapy with potassium chloride (until the fistula was closed)

Diarrhoea

Whatever the aetiology of the diarrhoea whether due to dysentery regional ileitis ulcerative colitis or any other cause there is a similar loss of water sodium potassium and chloride It is largely due to the pioneer work of Darrow on infantile diarrhoea that we owe our present knowledge of electrolyte disturbances and in particular of potassium deficiency

In many cases of diarrhoea there may be deficient intake due to apathy or

Disturbances of acid-base balance

The pH of the blood is dependent on the ratio between H_2CO_3 and HCO_3 Anything affecting the concentration of either of these two constituents of the blood will tend to produce a change in the pH Alterations of H_2CO_3 concentration are produced by respiration and are not of primary importance in gastro enterology A number of factors however, influence the HCO_3 concentration and thus the pH

These may best be considered by reference to Fig 247 which shows the change in the plasma concentration of various electrolytes under different circumstances The electrolytes are represented by two columns that on the left being the cations and that on the right the anions and as the number of cations must equal the number of anions these two columns must be equal This equality is usually maintained by adjustment in the amount of bicarbonate

WATER AND ELECTROLYTE DISTURBANCES IN SPECIFIC CONDITIONS

Pyloric stenosis

With pyloric stenosis can also be considered recurrent vomiting from any cause and continuous or frequent gastric aspiration as all of these conditions produce the same effect namely loss of large amounts of gastric fluid

A severe water deficit will result from these if water is not replaced by a route other than the mouth not only is all the water swallowed unabsorbed and lost in the next vomit or removed *via* the stomach tube but in addition the 1 000 millilitres of water per day from the water content of food is lacking

The gastric juice lost initially consists of an almost pure solution of HCl and this leads to a pure chloride deficiency and consequent alkalosis but the greater the amount of gastric juice lost the higher is the sodium and potassium content

In severe cases the sodium content of the gastric fluid may rise to half the chloride content This loss of sodium and potassium is probably due to the increased amounts of mucus produced by the irritated and inflamed mucosa Thus a loss of sodium and potassium is added to those of water and chloride Again the deficit is increased because the intake of these two ions is in the untreated case reduced to nil

This sodium deficit is responsible for one of the apparent clinical paradoxes of pyloric stenosis and allied conditions namely the excretion of an acid urine in the presence of a severe alkalosis The probable explanation is that the depletion of sodium is so great that there is none available for excretion as NaCl or $NaHCO_3$ and in the absence of fixed base the urine is acid (Van Slyke and Evans 1947) The administration of sodium chloride replaces this deficiency and allows the excretion of an alkaline urine

The potassium deficit in these cases is also responsible for another confusing clinical picture an alkalosis with hypochloraemia which is resistant to the administration of sodium chloride This syndrome is described by Nelson Friesen and Kremen (1950) in a woman with duodenal obstruction who had been maintained on parenteral fluids alone for fifty days and in whom the serum potassium had fallen to 0 98 mEq per litre According to Darrow (1948) when intracellular potassium is depleted and intracellular sodium is increased (as it is in a patient receiving no potassium but adequate amounts of sodium) biological

increases This if uncorrected will lead to a water deficit which may be increased by the sweating common at operation particularly in hot weather and when mackintosh sheets are used to cover the patient on the table

Sodium loss in a straightforward case is not great and although some sodium given in the post operative period to replace the small amounts lost improves the general condition more harm has probably been done by administration of excessive sodium parenterally than has resulted from sodium deficiency If however there is post operative vomiting sweating or if gastro intestinal suction is used a sodium deficiency can easily arise

As it is impossible to give adequate calories parenterally some tissue breakdown in addition to that directly due to the trauma of the operation always occurs This in addition to increasing the blood urea and consequently the obligate urine leads to the loss of the potassium in the destroyed cells

In addition to the impairment of renal efficiency the shock of the operation has another important effect Wilkinson and his colleagues (1949 and 1950) have shown that in the immediate post operative period there is sodium retention and a potassium excretion in excess of that attributable to tissue breakdown as measured by nitrogen excretion This is probably due to the release of adrenal cortical hormones as part of the alarm reaction for it has been shown that there is a fall in the absolute eosinophil count in the period of sodium retention and this is taken to be an indication of increased adrenal activity (Johnson and his colleagues 1950)

The potassium loss is also increased when large amounts of intravenous saline solution are given for this can wash out potassium from its intracellular position by substituting sodium

Thus the chief dangers of operation are water and potassium deficiency The risks of sodium and chloride deficiency or excess will depend respectively on whether there is excessive loss by the patient or excessive zeal on the part of the doctor

Alkali alkalaemia

This condition is far less common than previously now that the insoluble alkalis are more commonly employed in the therapy of peptic ulcer but it still occurs from time to time Only certain people appear liable to develop alkalosis following the ingestion of soluble alkalis for others can take large quantities with no ill effects

The chief symptoms are lethargy anorexia and mental changes there may also be vomiting headache muscle pains and polyuria and drowsiness may precede coma Tetany is less common than in other forms of alkalosis and it has been suggested that this may be due to the high blood level of magnesium sometimes found (Cope 1936)

The characteristic biochemical changes are a high bicarbonate a low chloride and an increase in the total base of the blood (Cope 1936) A small part of this rise in total base is due to an increase in the calcium and magnesium but it may not be present if there has been much vomiting

The picture may give the clinical impression of neurasthenia or of chronic nephritis with incipient uraemia

toxaemia which will augment the deficiencies produced by the excessive losses in the diarrhoeal fluid

In the acute cases with well marked dehydration the importance of adequate replacement therapy is usually realized but it is still too common to encounter cases of ulcerative colitis or other chronic diarrhoeas who have received adequate amounts of water but quite inadequate quantities of electrolytes Potassium deficiency has been described in ulcerative colitis by a number of observers for example Smith (1950) Posey and Bergan (1950) and in idiopathic steatorrhoea by Lubran and McAllen (1951)

Ulcerative colitis requires special mention for two reasons The hypoprotein aemia so often accompanying it makes the patient particularly likely to develop oedema if an excessive amount of sodium is given and in some cases it may not be possible to restore the sodium and chloride deficiencies as long as there is a protein deficit Secondly ACTH is claimed by some to have a beneficial effect on ulcerative colitis such therapy however carries with it a grave danger of potassium deficiency as in addition to the excessive faecal loss and possibly diminished intake that has already been mentioned in these cases there is an in creased loss in the urine for the effect of the hormone is to cause retention of sodium and increased excretion of potassium A fatal case of hypokalaemia in ulcerative colitis treated with ACTH has been described by Rossmiller Brown and Ecker (1951)

Intestinal obstruction and paralytic ileus

In both these conditions large quantities of fluid accumulate in the distended bowel and are not re absorbed This leads to a fall in the volume and concentration of the extracellular fluid and consequent water sodium potassium and chloride deficiency in the untreated case The removal of this fluid by intestinal suction will have all the effects of diarrhoea Moreover these deficiencies may establish a vicious circle for there is evidence that lack of both potassium and sodium may lead to lack of intestinal motility Streeten (1950) has shown experimentally in isolated rabbit guinea pig and human intestine that propulsive power and response to Prostigmin are impaired when the sodium and chloride concentration of the medium was reduced and he states that in humans no intestinal activity occurs and there is no response to Prostigmin if the sodium chloride concentration falls below 5 grams per litre He cites a case of paralytic ileus in which there was consistent response to the administration of hypertonic saline solution Webster Henrikson and Currie (1950) have shown that in rats potassium deficiency will produce paralytic ileus and Randall and his colleagues (1949) describe chronic ileus with moderate distension as one of the effects of potassium deficiency in surgical patients Eliel Pearson and Rawson (1950) also mention abdominal distension associated with potassium deficiency

Operations

Operation on the gastro intestinal tract creates a number of circumstances which can profoundly disturb metabolic equilibrium

In these cases it is often necessary to withhold all oral feeding for a time and due to starvation and consequent tissue breakdown the volume of obligate urine

Sodium excess—The classical sign of sodium excess is oedema but the increased extracellular fluid volume may be responsible for the development of signs of cardiac and respiratory distress Moreover an excessive sodium concentration in the extracellular fluid leads to withdrawal of water from the cells and this gives rise to thirst The increased volume of the extracellular fluid may be shown by a raised jugular venous pressure and this simple examination should not be omitted as it may be the first evidence of over treatment

Potassium intoxication—This is so rare in gastro enterological cases that it can be ignored

Potassium deficiency—A deficiency of potassium has been describ d as giving rise to two types of syndrome In a severe form there is gross muscular weakness and loss of peripheral reflexes The weakness may progress to paralysis of voluntary muscles and involve the intercostal muscles and the diaphragm A less severe form has been described by Randall and others consisting of drowsiness languor chronic ileus with moderate distension anorexia and weakness

It will be noted that a number of the signs and symptoms are common to many disturbances probably because it is almost impossible to have a derangement of one element of the extracellular fluid without concomitant changes in the others

The urine

Examination of the urine is of great importance in these cases Its volume specific gravity and chloride content should be noted In a pure water deficiency the urine will be small in volume of a high specific gravity and with a high chloride content In pure salt deficiency on the other hand it will be of normal volume of a rather low specific gravity and chlorides will be absent or greatly diminished Unfortunately bedside urine tests are of no value in estimating derangements of potassium metabolism It must be remembered that the chloride content is not always related to the sodium content

Laboratory findings

By considering the history examining the patient and testing the urine it should be possible to arrive at a diagnosis without laboratory tests A number of such tests are however of help in confirming the diagnosis and to some extent in assessing its severity It must be remembered that all estimations of electrolytes in the plasma are estimations of concentrations only and give no indication of the absolute excess or deficiency in the body as a whole The composition of the extracellular fluid is kept remarkably constant often at the expense of the intra cellular fluid and thus it is possible to have considerable disturbances of fluid and electrolyte balance without much alteration of the plasma concentrations Fortunately this control is not entirely perfect and plasma levels do indicate to some degree the alterations in the body as a whole

The haematocrit if the red-cell mass can be assumed to be normal is a useful and fairly accurate test for the volume of the extracellular fluid But the specific gravity of the serum (in the absence of hypoproteinaemia) will give more reliable information on the same point

The plasma alkali reserve (CO_2 combining power) will indicate any tendency to acidosis or alkalosis as long as there is no primary disturbance of respiration

ASSESSMENT OF DISTURBANCES

Before it is possible to carry out rational treatment of disturbances of body fluids and electrolytes it is necessary to diagnose the nature of the disturbances and assess their severity

This assessment should start in the same way as any other form of medical diagnosis that is with an adequate history This means considering the past intake and output of the patient and asking the question What has he been getting and what has he been losing?

Intake

Inquiry should be made about the intake of water electrolytes and food since the onset of illness If the patient has been taking a normal diet and normal amounts of water gross disturbances are unlikely to have arisen unless there has been excessive loss Too often inquiry is made only about the oral water intake but it has been stressed above that food in addition to supplying sodium and potassium in adequate quantities contributes a considerable amount of water and that starvation increases the obligate urine and also the urinary potassium excretion

In the absence of a normal amount of food it is likely that the patient has been receiving a deficient intake of sodium and potassium unless he has been fed parenterally in which case the amounts of these ions received can be easily calculated

Output

The urine output and the loss from vomiting gastric aspiration or intestinal suction can be easily measured In the case of diarrhoea and discharging fistulae this is not so easy and an approximation has to be made In general the amount of these losses is under estimated The amount of the various electrolytes lost can be calculated from a knowledge of the constitution of the lost fluid

In calculating the output the invisible loss must never be neglected and can be taken as a litre a day for most patients and 1½ litres daily for surgical patients with a greater allowance in warm weather

Finally a note should be made of any circumstance that may have reduced renal efficiency such as shock alkalosis or preceding renal disease

Condition of the patient

After investigating the past events the present condition of the patient should be considered

Water intoxication —This is extremely rare in this type of patient and can usually be easily diagnosed from the history it is characterized by throbbing headache hypertension and convulsions (Moyer Levin and Klinge 1947 Rowntree 1923) and may show itself as mental confusion simulating drunkenness

Water deficiency —The signs and symptoms of pure water deficiency are thirst dry tongue and skin sunken eyes and general weight loss oliguria mental confusion and vomiting

Sodium deficiency —A deficiency of sodium causes anorexia nausea vomiting muscle cramps general apathy and exhaustion (McCance 1936)

Manifestation		*Pure water depletion*	*Pure salt depletion*
Haemoconcentration		not till late and slight	+
Blood viscosity	–	normal till late	increased +[a]
Blood pressure	–	normal till late	fall +[a]
Water absorption	–	rapid	slow
Mode of death	–	? due to rise of osmotic pressure	peripheral circulatory failure

TREATMENT

The first aim of treatment should be to prevent any serious derangement arising The occurrence of any of the disturbances that have been described is a reflection on the primary handling of the case The best prophylactic measures of all are to give a normal diet and oral fluids as early as possible and as Evans (1950) says early withdrawal of all tubes from all orifices allowing ingestion of well cooked appetizing food even in small amounts and to observe what Francis Moore calls the need to be left alone All patients who have had experience of parenteral feeding will heartily agree with this

When the oral route is impracticable or inadequate sufficient intake can be given in a number of ways A gastric tube and drip feeding will by continuing the intake during the night often supply adequate water electrolytes and calories when these cannot be tolerated during waking hours

Rectal fluids can be used in many cases to supply adequate fluids and electrolytes

The subcutaneous route with hyaluronidase has been much used in infants but is infrequently used in adults as in the majority of cases intravenous therapy is easier and more reliable

Whatever the route of administration the basic daily requirements can be met by 3 litres of water (including water in food) 4–5 grams of sodium (as sodium chloride) and 2–4 grams of potassium This allows for an invisible loss of 1 500 millilitres and a urinary output of 1 500 millilitres The amount should of course be increased in hot weather and when a particularly large urinary output is desirable Thus 3 litres of one fifth normal saline solution will supply adequate water and more than adequate sodium but no potassium This can be added in a number of ways that are described later

To these basic amounts must be added a quantity sufficient to replace extra losses from gastric aspiration fistula fluid or vomiting If these losses are replaced by an equal volume of half normal saline solution equilibrium will be maintained except for potassium and when 1 gram of potassium is added to each litre of replacement fluid this will compensate for the average loss Potassium should however never be given where there is an inadequate urine volume

For the correction of an already established deficiency a number of empirical formulae have been devised for sodium and water

Coller and Maddock (1940) suggest the following clinical rule for each 100 milligrams that the plasma chlorides need to be raised to reach the normal (560 milligrams per cent) the patient should be given 0 5 gram of salt per kilogram of body weight

By far the simplest assessment is that of Phillips who uses the specific gravity of the serum and gives 200 millilitres of half normal saline solution for each

The plasma chloride level is often used as a measure of the sodium deficiency In general it is a moderately accurate guide as long as there has been equal loss or gain of sodium and chloride (that is if there is no change in the acid–base balance)

A more accurate idea of the sodium level can be obtained by combining estimations of plasma chloride and alkali reserve As Elkington Gilmour and Wolff (1939) have pointed out in the absence of ketosis renal damage or hypoproteinaemia the chloride and bicarbonate (measured as milliequivalents per litre) plus 27 milliequivalents will give an accurate figure for the total base As sodium provides by far the major portion of the base (143 out of the 155 milliequivalents) any marked change in the total of the acid radicals must demonstrate a change in the sodium concentration If the serum proteins are also measured the estimation is even more accurate

Thus the direct estimation of sodium which in the absence of a flame photometer is a lengthy investigation should rarely be necessary

The estimation of the potassium in the serum is also a time consuming investigation and unfortunately because of the small amounts present in comparison with odium no approximation can easily be made as in the case of the latter However the electrocardiogram can be used as a screening test for potassium deficiency The typical findings are flattening or inversion of the T waves prolongation of the Q–T interval sagging of the S–T segment low take off of the S–T segment and the appearance of a U wave (Smith 1950) Severe potassium deficiency does not seem to occur in the absence of electrocardiographic changes and as these are presumably due to intracellular disturbances they are probably a more reliable guide than estimation of the potassium concentration in the extracellular fluid in which for the reasons given above the changes may be minimal Plasma potassium levels can be used to confirm the electrocardiographic changes and as a measure of the severity of the deficiency

Distinctive clinical features

As water and salt depletion are the two most common disturbances in gastro enterology the following summary of the distinctive clinical features of these two syndromes as given by Marriott (1950) may be found useful It must be remembered that usually there is a mixture of the two types and that some of the features of salt depletion may be due to the deficiency of other ions than sodium

Manifestation	*Pure water depletion*	*Pure salt depletion*
Dehydration – –	$+^3$ primary or simple	$+^3$ secondary or extracellular
Thirst – – –	$+^3$	absent
Lassitude – –	+	$+^3$
Orthostatic fainting –	absent till late	$+^3$
Urine volume – –	scanty	normal till late
NaCl in urine –	often +	always absent except in Addison s disease
Vomiting – –	absent	may be $+^3$
Cramps – – –	absent	may be $+^3$
Plasma NaCl – –	slight increase or normal	diminished $+^3$
Blood urea – –	+	$+^3$
Plasma volume –	normal till late	decreased $+^3$

integer that the specific gravity is raised above 1 027 for example if the specific gravity is 1 037 2 000 millilitres are given (1 litre of normal saline solution and 1 litre of 5 per cent dextrose in water) This is dependent on the plasma proteins being normal and assumes that there is a mixed water and sodium deficit as occurs in the majority of gastro-enterological patients By the use of the chart given in Fig 248 (Bull 1951) it is possible to correct the major part of the dehydration and also any acidosis present rapidly and with safety

After an initial rough correction has been made by this method finer adjustments can be carried out after more detailed investigation It should be emphasized that rapid correction of these states is often necessary the requisite fluids being given in two or three hours

For the treatment of sodium excess it is usually adequate to restrict the sodium intake and mercurial diuretics are rarely required

For the treatment of potassium deficiency no such empirical rules have been devised and the amount necessary to restore a deficit has varied very greatly in the cases reported Again it must be emphasized that potassium should not be given unless there is an adequate urine volume

For oral use one can use a mixture of equal parts of potassium acetate bicarbonate and citrate 4 grams of each made up to 100 millilitres with water Fifteen millilitres of this mixture are given 4 times daily (Randall and his colleagues 1949) Alternatively 1 gram of potassium chloride in capsules 4 times daily can be given (Eliel and others 1950)

For intravenous use potassium chloride can be added to the perfusing fluid The strength should not be too great as the concentration in the blood reaching the heart should not exceed 7 mEq per litre If 2 23 grams of KCl are given in a litre of 5 per cent dextrose (Randall and his colleagues 1949) and this is given at a rate not exceeding 1 litre in an hour there should be little danger unless there is marked renal damage

Thus the treatment of disturbances of fluids and electrolytes in gastro-enterological cases can be summarized as

(1) Prophylaxis
(2) Accurate diagnosis
(3) Accurate replacement

Of these the first is by far the most important and few misadventures would arise if physicians were constantly to ask themselves over each case What is this man getting and what is he losing?

REFERENCES

Bull C M (1951) Personal communication
Coller F A and Maddock W G (1940) *Surg Gynec Obstet* 70 340
Cope C L (1936) *Clin Sci* 2 287
Darrow D C (1948) *J Clin Invest* 27 198
Denton D A (1949) *Med J Aust* 2 521
Eliel L P Pearson C H and Rawson R W (1950) *New Engl J Med* 243 471 and 518
Elkington J R Gilmour M T and Wolff W A (1939) *Ann Surg* 110 1056
Evans E I (1950) *Ibid* 131 945
Fuge W W and Hogg B M (1938) *Ibid* 108 1

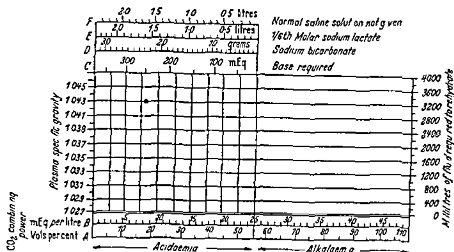


FIG 248 —*If the patient is thought to be dehydrated and if the serum protein con* centration before dehydration can be presumed to have been normal determine the plasma specific gravity (left hand vertical column) and read off in the right hand vertical column the volume of fluid corresponding to the value obtained (volume of fluid necessary to rehydrate) This volume of fluid should be given as half normal saline solution (alternate bottles of normal saline solution and 5 per cent glucose without saline)

If at the time the patient has a disturbance of acid–base balance determine the CO_2 combining power (Scale A or B) If the reading is to the right of the central vertical line the patient can be presumed to be alkalaemic and rehydration with saline solution and water is all that need be done If the reading is to the left of the central line the patient can be presumed to be acidaemic In addition to fluid a quantity of base is then required to correct the acid–base balance The amount of base necessary to correct the acid–base balance in the extracellular fluid is shown in Column C *This may be given as sodium bicarbonate and the amount required* is shown in Column D or it may be given at 1/6th molar sodium lactate which is shown in Column E If the base is necessary less NaCl must be given than deter mined from the vertical column or else the patient will be given a total excess of ions The amount of normal saline solution which is subtracted from the amount required to rehydrate is shown in the top of Column F

Both the specific gravity and CO_2 combining power determinations should be repeated *after the administration indicated and further correction may be necessary*

In the example shown the pla ma specific gravity is 1 043 This patient requires 3 200 millilitres of fluid to rehydrate him This would be given as 1 600 millilitres of normal saline plus 1 600 millilitres of 5 per cent glucose solution

He is however also acidaemic (CO_2 combining power 8 mEq per litre) and requires about 260 mEq of base to correct the acid base balance in 15 litres of his body fluids (that is 1 extracellular fluid volume) This could be given as 22 grams *of sodium bicarbonate or approximately* 1 6 litres of 1 6th molar sodium lactate In either event 1 7 litres of normal saline solution should not be given This is a little more saline solution than prescribed but only very little

The final infusion would therefore be 1 600 millilitres 1 6th molar sodium lactate plus 1 600 millilitres of *5 per cent glucose solution*

(By courtesy of Dr G M Bull)

CHAPTER 30

DIFFERENTIAL DIAGNOSIS OF JAUNDICE THE USE OF *LIVER BIOPSY AND LIVER FUNCTION TESTS*

W E King

'There must be few sections of medicine around which a larger literature has grown up than the pathology of different forms of jaundice These words written 27 years ago by McNee still hold true today and it is fitting that the words of a man who has done so much to clarify our ideas on this subject should be quoted The most useful classification of jaundice at the present time is still that of McNee

Jaundice is best defined as that condition in which an excess of bilirubin accumulates in the blood with a resultant discoloration of the skin mucosae and sclerae In the main jaundice may be regarded as a symptom of disease of the liver and its biliary system since as will be discussed later evidence is accumulating that even in haemolytic disease damage of some form to the liver is necessary for the production of clinically detectable jaundice

Pathogenesis of jaundice

The circulation and excretion of bile in the body occurs in three main steps (a) manufacture by the reticulo endothelial cells (b) excretion of the pigment into the bile by the liver cells and (c) passage *via* biliary system into the intestine where bilirubin is converted to stercoblin and finally excreted from the body It can therefore be seen that disturbance of any one of these steps could lead to jaundice

Excessive manufacture of bilirubin due to excess haemolysis so overtaxing the excretory powers of the liver that hyperbilirubinaemia results —This is the current theory to explain the mechanism of haemolytic jaundice Rich (1930) regards this as a very rare cause of jaundice and his views are supported by McMaster and Rous (1921) who occluded the ducts from 95 per cent of the liver of a dog without producing jaundice Further evidence of this state of affairs can be readily obtained from autopsy specimens where the liver may be extensively replaced by malignant tissue without jaundice appearing It seems probable that where jaundice occurs with excessive haemolysis the anoxia or the anaemia so produced has damaged the liver cells Of course in some cases the haemolytic agent causes direct damage to hepatic tissue

Injury to the liver cells by infection or toxic agents to such an extent that they are unable to excrete the bilirubin normally formed —Where this injury is severe enough to produce necrosis it is easy to see how bile retention occurs but quite often pigment retention can be seen in biopsy specimens where cell necrosis is absent The bile is seen in the liver cells and between the cells suggesting it is some alteration in the cell itself that is causing the hold up Pressure of swollen liver

Gamble J L (1947) *Chemical Anatomy Physiology & Pathology of Extracellular Fluid* Cambridge Mass Harvard University Press
Johnson H T Conn J W Iob V J and Coller F A (1950) *Ann Surg* 132 374
Leaf A and Camara A A (1949) *J Clin Invest* 28 1526
Lubran M and McAllen P M (1951) *Lancet* 1 321
McCance R A (1936) *Ibid* 1 643
Marriott H L (1950) *Walter and Salt Depletion* Springfield Ill Thomas
Moyer C A Levin M and Klinge F W (1947) *South Med J* 40 479
Nelson R M Friesen S R and Kremen A J (1950) *Surgery* 27 26
Posey E L and Bergan J A (1950) *Gastroenterology* 16 39
Randall H T Habif D V Lockwood J S and Warner S C (1949) *Surgery* 26 341
Rossmiller H R Brown C H and Ecker J A (1951) *Gastroenterology* 17 25
Rowntree L G (1923) *Arch intern Med* 32 157
Smith F H (1950) *Gastroenterology* 16 73
Streeten D H P (1950) *Surg Gynec Obstet* 91 421
Van Slyke K E and Evans E I (1947) *Ann Surg* 126 545
Webster D R Henrikson H W and Currie D J (1950) *Ibid* 132 779
Wilkinson A W Billing B H Nagy G and Stewart C P (1949) *Lancet* 1 640
— — — — (1950) *Ibid* 2 135

cases these alone will enable the correct diagnosis to be made when laboratory aids are used merely as confirmatory evidence

Haemolytic jaundice is excluded by the family history presence of crises lack of bile in the urine and normal coloured faeces In addition an enlarged spleen will often be found on physical examination Further evidence will be provided by the presence of spherocytes reticulocytes increased red cell fragility or in the acquired form by the presence of a positive Coombs test Increased uro bilinogen in the urine and stercobilinogen in the faeces will also help but are not usually necessary for the making of the diagnosis The remainder of the discussion will be concerned with the differentiation of the hepatocellular and obstructive types of jaundice

History

Contact —A history of contact with a case of jaundice may be of real value Unfortunately when dealing with infective hepatitis it is not often obtained unless there is an epidemic Recently in Melbourne there have been two endemic foci of this disease and knowledge of this has sometimes helped in making the diagnosis

Occupation and environment —It is always worth while to obtain some idea of the patient s dietary habits and while this may not be readily achieved persons who live a solitary existence are more likely to show dietetic deficiencies A history of working in the liquor trades may pre suppose a diagnosis of cirrhosis but can only be used as suggestive evidence Sewer workers fish handlers and cane cutters are more exposed to Weil s disease than ordinary members of the community Exposure to certain industrial poisons may also be discovered

Past history —A previous attack of painless jaundice during earlier life will suggest chronic infective hepatitis or cirrhosis as the underlying cause The history of recurrent painful episodes of jaundice is strongly in favour of gall stones Some times this history may be obtained in cases of carcinoma of the gall bladder which is so often associated with cholelithiasis Careful inquiry for the taking of drugs recent injections or transfusions should never be omitted

Age —While infective hepatitis is most often a disease of children and young adults its presence in the older age group has been observed This appears to have followed its increased prevalence in the post war years Cirrhosis too as a cause of jaundice has to be considered in the older patients but only after every care has been taken to exclude some superadded cause for the jaundice by clinical bio- chemical and even histological means Until this is realized autopsies will continue to show a calculus in the lower biliary tree However the commonest cause of jaundice in the aged is carcinoma obstructing the bile-duct

Duration of jaundice —Before the advent of liver function tests and biopsy the surgical rule was to perform a laparotomy on jaundiced patients after 6 weeks This of course excluded the majority of cases of hepatitis Usually the duration of jaundice in these subjects is 2–3 weeks carcinomatous obstruction persisting without any real fluctuation With modern operative procedures for radical cure of carcinoma of the pancreas or bile-ducts it is better not to wait for as long as this particularly as it has been shown that cholangitis rapidly follows obstruction to the bile-ducts

Presence of pain —Pain may occur in infective hepatitis usually of a dull aching

M T Gas E t—43

cells on the intralobular canaliculi has been the favourite theory to explain this phenomenon, but one should be cautious in accepting a pressure theory in an organ as largely distensible as the liver

There remains a group of cases in which no cause can be discovered for a mild degree of hyperbilirubinaemia The symptoms of which these patients complain are no more than would be found in a control group of normal individuals While this is a small group such cases have been described from various centres all over the world This condition has been carefully described by Dameshek and Singer (1941) who suggested some alteration in permeability of the hepatic cells as a cause Meulengracht (1947) has collected a series of such cases and has followed them for a period of up to 36 years The jaundice is usually worse with fatigue or alcoholic excess All investigators have carried out liver function tests while Krarup and Roholm (1941) have shown the liver to be histologically normal on biopsy Values for faecal stercobilinogen are normal or even low

Recent work by Mollison (1948) has shown that jaundice occurring in the new born (physiological jaundice) is due to functional immaturity of the liver cells and not as had been previously thought an excessive haemolysis of the red blood cells soon after birth He confirmed this by demonstrating that the rate of brom sulphalein excretion in the new born was slower than in the adult

Disruption of the biliary system by the increased pressure of obstruction to the outflow of bile so allowing a re absorption of bile into the general circulation after it has passed through the liver cells—This mechanism is the easiest of the three causes of jaundice to explain since it rests entirely on a mechanical obstruction

Classification of jaundice

The two classifications of jaundice most often used are those of Rich (1930) and McNee (1923) Rich claimed that his classification was based on pathogenesis and overcame the criticisms launched against previous divisions into obstructive and non obstructive He divided jaundice into two types Retention jaundice and Regurgitation jaundice This means that two of the commoner causes of jaundice hepatitis and mechanical obstruction are contained in the same group In reality it seems that Rich s classification suffers from the same defects that he criticized in others that is it lacks specificity

On the other hand McNee (1923) divided jaundice into three main groups (a) obstructive (b) toxic and infective and (c) jaemolytic Usage of the term hepatocellular has now been substituted for the group labelled toxic and infective Criticism has been levelled at this classification because examination of biopsy and autopsy material has shown mechanical obstruction as well as necrosis in infective hepatitis also because the same examination of material from cases of mechanical biliary obstruction shows cholangitis and damage to liver cells No one can deny that this does occur but in the main this classification is the most useful clinically and has stood the test of time

Differential diagnosis

No amount of biochemical and histological investigation can replace the clinical history and examination in unravelling the problem of jaundice In the majority of

admixture of pigments since melanin metabolism may be upset in chronic liver disease

Other skin changes—The presence of vascular naevi (spiders) should be carefully sought These occur mostly on the face chest and upper limbs—it is uncommon to find them elsewhere While their presence has been noted in pregnancy deficiency diseases and normal people it is most common to see them in chronic and extensive liver disease They appear to be the result of an upset in oestrogen metabolism and are most often seen in chronic hepatitis and cirrhosis Their association with abnormal oestrogen metabolism has been well shown in a case of severe hepatitis recently Coincidentally with improvement in jaundice in this patient the menses reappeared and at the same time there was fading of the vascular naevi Sometimes they are seen with extensive liver destruction due to secondary carcinoma and in patients with prolonged obstructive jaundice in whom the ensuing cholangitis has led to liver cell injury

Palmar erythema (liver palms) is another skin lesion which may be helpful This is a distinct zone of erythema spreading from the hypothenar eminence across the base of the metacarpals to the thenar eminence Its aetiology seems associated with a lowered serum albumin content If present it also favours the diagnosis of parenchymal damage in the liver

Breath—A peculiar sickly sweet odour in the breath occurs in cases of severe hepatitis chronic hepatitis and actively progressing cirrhosis This is best likened to the smell of a freshly cut cirrhotic liver at autopsy It has been dubbed foetor hepaticus by workers in the United States of America Its presence is useful both for diagnosis and prognosis In a recently studied series of cases of chronic hepatitis this odour was detected in all the fatal cases and at some time in nearly all the ones that recovered

Lymphadenopathy—A careful search should always be made for enlarged lymph glands Generalized enlargement occurs sometimes with infective hepatitis Glandular fever can cause a hepatocellular type of jaundice and biopsies have shown liver damage similar to that in infective hepatitis Occasionally leukaemia and Hodgkin s disease may be the primary agent in jaundice without any previous manifestations The importance of Virchow s gland in the left supra clavicular region is so well known as to require no further discussion

Palpable liver—The liver edge is frequently palpable in normal people Further a liver easily palpable clinically may be found to be shrunken at autopsy particularly in cases of cirrhosis The degree of hardness of the enlarged liver is helpful—a hard liver usually being associated with metastases or cirrhosis If obstructive jaundice has been present for over 2 months the liver may become quite firm due to fibrotic changes following cholangitis

More difficulty is experienced in assessing whether the enlarged liver is smooth or nodular but if nodularity is found it is suggestive of metastatic involvement At times in chronic hepatitis multiple nodular hyperplasia can be detected on clinical examination and care must be taken not to confuse this with secondary nodules Occasionally a friction rub may be found usually this occurs with a neoplastic nodule near the surface It is worth noting that this friction may be associated with severe pain This may be of sufficient severity to lead to a diagnosis of an acute abdomen

or dragging character Occasionally it may be quite sharp in nature and radiates to the back Similar sharp pains have also been seen in cirrhosis *where due to some* nutritional upset there has been a sudden increase in the size of the liver Carcinoma of the pancreas is not usually a painless disease—75 per cent of cases of this condition have a history of pain usually of a boring character and radiating to the back It is often severe and relief may be obtained by alteration *of posture When* painless jaundice is due to malignancy it is more often due to carcinoma of the bile ducts or ampulla of Vater than to carcinoma of the pancreas (Whipple, 1945) Pancreatic pain may at times be colicky and mimic gall stone colic The *presence of colicky attacks of* pain *should* suggest the presence of gall stones though this pain may not be confined to the right hypochondrium—in some it may be located in the epigastrium and occasionally is felt to the left of the mid line or in other areas of the abdomen The radiation may be that of pancreatic pain though usually some radiation to the right scapular region can be elicited

Hydatid cysts in the liver may sometimes be associated with pain either colicky due to passage *of material down the ducts or radiating to the right shoulder* An important point in the diagnosis of hydatid disease sometimes overlooked is a history of skin rashes usually of an urticarial nature This has to be remembered when dealing with patients who have lived in endemic areas

Gastro intestinal symptoms—The history of anorexia nausea and epigastric discomfort preceding jaundice immediately suggests the diagnosis of hepatitis This may prove particularly helpful in the middle aged or older patients However anorexia may be a premonitory symptom of carcinoma or cirrhosis

Just as important is the fact that common duct stone does occur without any history of flatulent dyspepsia though often a history of digestive upsets can be obtained Diarrhoea is very common in chronic hepatitis It occurs during a recrudescence of the disease *It may be present in any case of obstructive jaundice* due to malabsorption of fats but its presence in middle age should point to a pancreatic lesion Melaena if present is of very real help in making a pre operative diagnosis If blood in occult form be excluded the diagnosis to be considered is carcinoma of the ampulla of Vater since this is the most favourable neoplasm for radical surgery Unfortunately carcinoma of the stomach with secondaries in the liver or carcinoma of the pancreas eroding the duodenum may also give this *clinical picture*

Physical examination

The examination of the jaundiced patient often gives the key to making an accurate diagnosis The finding of a mass indicative of a primary *carcinoma with* metastases in the liver will not be discussed any further The importance of examination lies in being able to differentiate hepatocellular from obstructive jaundice The following points will be helpful in this respect

Degree of jaundice—This is often very difficult to assess clinically but neoplastic obstruction commonly leads to a darker greenish yellow coloration This has to be distinguished from the more yellowish appearance of hepatocellular jaundice In *chronic hepatitis* the pigmentation approaches closely that seen in neoplastic jaundice This darkening of the skin in chronic hepatitis is almost certainly an

be dangerous However recent work in the United States of America has shown that where the total serum bilirubin is less than 11 0 milligrams per cent and the retention of bromsulphalein less than 30 per cent, a gall bladder shadow could be obtained in 90 per cent of cases (Readinger and others 1950) The material consisted of 43 cases of infective hepatitis These workers further qualify their conclusions by advising a double dose of dye if the total serum bilirubin is over 5 milligrams per cent and bromsulphalein retention over 15 per cent No toxic results were noted in this study These results may be of considerable clinical value in the differentiation of painless jaundice in the middle aged or elderly patient but require more extensive trial

Examination of the blood—This may exclude such causes as glandular fever and leukaemia The leucocyte count in hepatitis is low and tends to be elevated in obstructive jaundice particularly when cholangitis develops The highest white cell count is seen in secondary carcinomatous involvement of the liver particularly when necrosis is occurring Eosinophilia may suggest parasitic disease

Casoni test—When any suspicion exists of the patient having lived in an area where hydatid disease is endemic this test should always be done If the result is doubtful a hydatid complement fixation test is also carried out

Wassermann reaction—Syphilis as a cause of jaundice is rare in modern times Occasionally a case will be seen Care should be taken in evaluating a weak positive reaction which may occur in infective hepatitis following increase in serum globulin

LIVER BIOPSY

This procedure which was first described by Lucatello in Italy in 1895 has now emerged from the experimental stage It has proved to be a useful adjunct in the diagnosis of cases of jaundice where clinical and biochemical findings are equivocal In the majority of such cases the type of jaundice can be determined by careful study of the histological material Its usefulness is not restricted to cases of jaundice and at the present time liver biopsy would seem to be of greatest value in diagnosing the cause of liver enlargement

The modern era of liver biopsy began in 1939 when Iversen and Roholm (1939) reported their results in 160 biopsies without any fatalities It was only natural that the procedure should have been accepted with some caution but over the past 4 years numerous reports from all over the world have testified to the value of biopsy During the period 1939–44 most interest was shown in following the pathology of hepatitis

Various techniques and needles have been described and in the United States of America the site of inserting the needle has been the subject of debate for some time The safest needle is the Franseen type which was used by Iversen and later by Sherlock This has the disadvantage of a small bore (internal diameter 1 millimetre) and therefore difficulty may be encountered in obtaining an adequate specimen from a cirrhotic liver To outweigh this disadvantage is the small number of post biopsy complications following the use of this needle Most workers in the United States of America prefer the Vim Silverman needle which has a mechanism for biting out a piece of liver tissue more in line with biopsy forceps in other areas

The actual size of the liver is not always a reliable guide but usually infective hepatitis does not cause as great an enlargement as carcinomatous obstruction The liver in the former condition usually enlarges 2–3 centimetres below the costal margin In the latter it may be found to extend to the level of the umbilicus Hydatid disease with jaundice may cause a moderate degree of enlargement quite often affecting both lobes due to multiple cysts

On the other hand when the liver is not palpable hepatitis or cirrhosis is the most likely cause

Gall bladder enlargement —The presence of a palpable gall bladder is one of the most useful clinical signs when present It nearly always means neoplastic obstruction but can occasionally occur with calculus obstruction Unhappily the absence of an enlarged gall bladder cannot be used so definitely in making a diagnosis as its presence None the less the presence of a painless jaundice in the absence of a palpable gall bladder has often been associated with a carcinoma of the bile duct which involved the cystic duct This type of carcinoma seems to be more common in males

The gall bladder may not be palpable at every examination and it is worth while repeating this procedure daily in cases of obstructive jaundice At times the gall bladder may distend to an enormous size and be felt as a large cystic swelling in the right iliac fossa Occasionally during distension the gall bladder changes its axis and can then be felt lying almost transversely Rarely the distended gall bladder may be tender

Splenomegaly —The presence of a palpable spleen is a most valuable sign in the clinical diagnosis of jaundice When haemolytic disease is excluded an enlarged spleen usually means acute or chronic hepatitis or cirrhosis If obstructive jaundice is of long standing the spleen may become palpable due to the development of a biliary cirrhosis

Caution is necessary in assessing splenomegaly in acute hepatitis In this disease the spleen if palpable is soft and felt just below the left costal margin The finding of a spleen 3–4 centimetres below the ribs should suggest the presence of some other disease In the last three cases I have seen with such a degree of splenic enlargement the diagnosis has been acute leukaemia glandular fever and Hodgkin s disease respectively

Ascites —The finding of ascites in a jaundiced patient naturally points to cirrhosis or peritoneal involvement by metastases In massive necrosis of the liver the onset of ascites is sudden and the fluid accumulates rapidly

The presence of dilated veins particularly on the right side of the abdomen is most often seen in cirrhosis They may occasionally follow obstruction to the portal vein by a pancreatic tumour

Investigations

Radiology —A plain radiological examination of the liver area should be done in all cases of jaundice where the diagnosis is in doubt It may reveal the presence of gall stones hydatid cysts or the dense shadow of the liver of haemochromatosis though the last named is rarely a cause of jaundice except occasionally in the terminal stages Cholecystography is usually contra indicated in the presence of jaundice A satisfactory concentration of dye will not be obtained and it may even

radiograph of the liver area immediately before biopsy This is most necessary when there has been a previous operation in this region and the bowel is adherent to the liver In areas where hydatid disease is endemic an intradermal test (Casoni) for this disease is a wise precaution It is necessary to know the patient s blood group and to have facilities for transfusion at hand

Technique of liver biopsy

The patient lies supine in bed with the right arm raised above the head Skin and intercostal tissues are infiltrated with 2 per cent Novocain solution in the ninth intercostal space usually in the mid axillary line Care must be taken to infiltrate the diaphragm and the capsule of the liver After a lapse of 3 minutes for anaesthesia a small snick is made in the skin and the biopsy needle inserted at right angles to the skin The patient is told to stop breathing and the needle is inserted into the liver When well inside the right lobe the trocar is withdrawn and the cannula advanced with a rotating motion to cut out the specimen of liver Next the syringe is attached and suction applied On withdrawal of needle and syringe *the biopsy material is found floating in the syringe* With *reasonable experience* the time taken for the actual biopsy should be less than 10 seconds This is important for the patient who has to hold his breath In most cases some blood is aspirated as well but this does not seem to cause any damage and is not an indicator of subsequent bleeding

If the subcostal route should be used the technique is much the same with regard to anaesthesia except of course this route avoids the diaphragm This has the advantage of not requiring the patient to hold his breath It cannot be too strongly stated that the liver is a shelving organ when it enlarges therefore for safety by this route the liver should be palpable at least 3 centimetres below the right costal margin

In most patients it should not be necessary to use a sedative before biopsy—I have not used it as a routine preferring to give morphine 1/6 grain immediately afterwards

After-care of liver biopsy

An accidental discovery while perfusing a liver has led to a great diminution in post operative pain and complications This was largely due to J W Perry (Pathologist at the Children s Hospital Melbourne) It was noted that in a liver being perfused at almost normal hepatic artery and portal vein pressures pieces could be removed with impunity provided the liver was not moved If movement occurred a jet of perfusing fluid appeared at the site of puncture Accordingly absolute immobility of the trunk and lower limbs is demanded for 2 hours after biopsy and as a result post operative pain has been greatly reduced After this strict bed rest is enforced for the next 24 hour and the patient kept in hospital for a total of 48 hours

Should severe pain occur at the site or in the shoulder further morphine is given Dull aching pain will be found to occur in about 25 per cent of cases but this responds to analgesics by mouth The charting of the pulse hourly should be carried out for 24 hours

Any sign of bleeding which is always heralded by severe pain and a rising pulse

of the body This will certainly produce a larger number of adequate sections of tissue in a cirrhotic liver The latest modification is the Gillman needle which is incorporated with a 20 millilitre syringe The stilette is fitted to the plunger of the syringe This combination saves time in carrying out the various manipulations necessary for biopsy The recent reports on this needle claim a lower percentage of failures and also that fragmentation of the specimen is lessened

It seems all three needles have their advocates—the writer has always used the Franseen needle and has obtained satisfactory results In any decision on the virtues of a particular type of needle it must be remembered that the experience of the operator counts for a great deal In all reported series the percentage of failures diminished as the number of biopsies increased

The site of the puncture has also been the subject of controversy Iversen and later Sherlock used the intercostal approach which is still the common route This means the patient must be co operative and able to hold his breath during the actual puncture of the liver and obtaining of the specimen Topp and others (1948) have claimed that the intercostal route is too dangerous yet the series reported by Sherlock (1945) Cogswell and Schiff and others (1949) Volwiler and Jones (1947) van Beck and Haex (1943) were nearly all by this route The un fortunate accident of perforating the colon or duodenum has always been by the subcostal approach Surprisingly this complication has not so far proved fatal From personal experience of both methods in 200 cases I can say that the subcostal route is easier since breath holding is not obligatory and more time can be taken in obtaining the tissue At the same time it is not a safe method unless the liver is enlarged at least three centimetres below the costal margin Certainly if possible it is the route of choice if the presence of metastases is being sought as a nodule may be selected for biopsy so lessening the chances of obtaining unaffected liver tissue It is also the route that should be used in young children

The technique has been so adequately and so often described that it will only be briefly discussed It is always necessary to have the patient in hospital and all care should be taken to minimize the awe engendered in the patient For this reason it should be done as a ward procedure Adequate local anaesthesia is essential not less than 10 millilitres of 2 per cent Novocain should be used More of the patient

Pre operative management of liver biopsy

The two complications to be feared are bleeding and perforation of the bowel The former can be obviated by estimating the prothrombin time and making sure this level is above 70 per cent by giving vitamin K intramuscularly in doses of 10 milligrams daily If the prothrombin level fails to rise and biopsy is still considered necessary a transfusion of fresh blood will make the procedure much safer Stored blood should not be used as its prothrombin content falls quickly It is better to avoid biopsy on anaemic patients as bleeding may follow—if the investigation is necessary transfusion should be given before and during the procedure Naturally if there be any suspicion of a bleeding disease coagulation and bleeding times are done The second complication of perforation of the bowel is avoided by a plain

its amount (b) presence or absence of necrosis (c) presence or absence of liver cell regeneration and architectural disturbances and (d) changes in the portal tracts

(i) type of cell present and its relation to the bile-ducts
(ii) bile-duct proliferation and
(iii) distribution of the fibrous tissue

Other indications for liver biopsy

Hepatomegaly —At the present time liver biopsy is probably more useful for deciding the cause of this than in any other sphere An inactive cirrhosis is quite a common cause of liver enlargement—this will usually not be detected by ordinary liver function tests Since using liver biopsy over 20 cases of haemochromatosis have been diagnosed in the past 4 years in Melbourne In the past 7 months the writer has proved 6 cases of haemochromatosis by this method

Fatty changes in the liver following malnutrition or alcoholism will be readily detected—it also provides a useful guide to therapeutic response in this disease This will be discussed later

Invasion of the liver by carcinoma Hodgkin s disease and leukaemia may also be detected However the presence of unaffected liver tissue at biopsy must not be taken as certain evidence against these conditions It is only of value when a positive result is obtained

General systemic disease —Scadding has drawn attention to the value of liver biopsy in diagnosing sarcoidosis It is well to heed the warning in the article by Scadding and Sherlock (1948) and make sure the embedded block of tissue is cut at several levels or a high proportion of negative results will be obtained Brucellosis is another disease where distinct lesions in the liver may be found at biopsy In insulin resistant diabetics biopsy may show fatty changes in the liver Kala azar and schistosomiasis have also been diagnosed by this method Amyloid disease may be found at biopsy but care must be taken in performing biopsy as splitting of the liver has followed biopsy in an amyloid liver In obscure anaemias the presence of extramedullary haemopoiesis in the liver may be found leading to a diagnosis of myelosclerosis or some similar state

As a pre operative measure —In portal hypertension liver biopsy may tell whether the obstruction is extrahepatic but I have not found this method very reliable Some workers claim liver biopsy should be done in constrictive pericarditis before operation The changes in this condition are non specific and not much help will be obtained from the procedure In malignant disease where metastases are suspected a positive biopsy finding will be helpful

In assessing prognosis —Biopsy is particularly useful in cases of chronic hepatitis If regeneration is active and necrosis minimal or absent a much better prognosis can be expected Similarly in assessing the response to treatment in nutritional disease of the liver biopsy is most useful In cirrhosis of the liver the degree of activity as judged by the cellularity of the portal tracts and the invasion of the liver lobules may be a very useful guide to further management of the case

As an experimental procedure —No one can doubt its value in elucidating some of the problems of hepatic disease It is still a very useful tool for clinical research and with the increase in histochemical methods further valuable results can be expected

rate should be treated with transfusion This is rarely necessary and in my experience has occurred only twice in 200 cases

Mortality of liver biopsy

The figures collected by Terry show a mortality rate of 0 28 per cent in nearly 2 500 reported biopsies In the Clinical Research Unit at the Royal Melbourne Hospital 500 biopsies (including my own 200) have been performed without any deaths These figures are additional to those quoted by Terry

The value of biopsy in jaundice

In the majority of cases of jaundice liver biopsy should give the correct diagnosis Bjørneboe Iversen and Keiding (1949) in reviewing experience with 1 600 cases of jaundice state that there are clear indications for biopsy in 4 per cent of medical material and 13 per cent of surgical material These percentages are those cases where a thorough history and clinical examination plus adequate biochemistry did not give the correct diagnosis In the medical material the percentage of uncertainty fell from 4 to 0 4 per cent by the use of biopsy For a start the interpretation of the histological material may be difficult but with reasonable experience differentiation between obstructive and hepatocellular jaundice should be possible If available the frozen section technique is helpful as it allows the pathologist to see the exact situation of the bile pigment in the section Usually in formalin fixed material a certain amount of bile is washed out of the section and this is even more so when Masson s fixative is used

In obstructive jaundice the outstanding feature of the section is the amount of bile pigment seen This is to be found in the central zone of the liver lobule and is contained in the parenchymal cells as well as appearing to plug the intralobular canaliculi in this area The liver cell architecture is normal and any increase in fibrous tissue is in the portal tract region Many new bile duct elements may be seen and if the obstruction has been present for any time there will be an increase in inflammatory cells These show quite a large number of polymorphonuclear leucocytes and tend to be arranged in relation to the bile ducts Evidence of liver cell hyperplasia or necrosis is usually absent but sometimes may be seen at the periphery of the lobule

In infective hepatitis there may be seen centrilobular polygonal cell necrosis or if later in the disease evidence of regeneration of the liver cells particularly near the central vein Wandering cell infiltration is usually seen to some degree and will be found in the portal tracts and also between the columns of liver cells Some increase in young fibrous tissue may also be seen The bile pigment will be scattered more diffusely through the section though some plugging of the intralobular canaliculi will be seen at times

In chronic hepatitis the section will show islands of hyperplastic liver cells tending to a concentric arrangement These are surrounded by moderately vascular fibrous tissue containing mononuclear cells and usually an increased number of bile ducts Sometimes necrosis in the regenerating areas can be seen The islands of regeneration will be found to vary greatly in size

The important points in differentiating obstructive and hepatocellular jaundice in the examination of biopsy material are (a) the site of the bile pigment and

(1946) Roberts (1933) Corkhill and others (1946) Gray (1947) has shown that the so-called biphasic reaction is not due to the presence of two forms of bilirubin but to the failure of strong solutions of azo bilirubin to follow Beer s law He further states that there is no evidence of the existence of direct and indirect bilirubin as separate entities The value of the quantitative test is however twofold it allows of the detection of jaundice before it is manifest at the bedside Secondly the course of a jaundiced patient s condition can be followed quantitatively by serial estimations Although great variation in values can be seen patients with carcinomatous obstruction tend to have the highest values

Icterus index

This is both inaccurate and unnecessary in view of the ease with which a quantitative van den Bergh reaction can be carried out

Bilirubin tolerance

This procedure naturally cannot be used in the jaundiced patient. It is expensive and may be painful if the material escapes from the vein (due to the action of the solvent) It has been claimed as a sensitive index to liver dysfunction in pregnancy and cirrhosis but is seldom performed at present

Urobilinogen in urine and faeces

This comparatively simple and often neglected test may be of definite value in the differential diagnosis of jaundice The usual method of estimation is by the technique of Wallace and Diamond though some may prefer Watson s method The latter is a more painstaking procedure and gives a more accurate result Its use is not necessary in ordinary clinical laboratories The absence of urobilinogen from the urine is strongly in favour of a neoplastic type of obstructive jaundice The variations in urinary urobilinogen follow closely the course of infective hepatitis

In suspected chronic liver disease the detection of increased amounts of urinary urobilinogen may be of distinct help

Faecal stercobilinogen is not so widely used except in suspected haemolytic disease Here the presence of excess amounts of pigment may be an aid to diagnosis

Galactose tolerance test

Owing to the slightly complicated procedure necessary this has not been used as a routine in Melbourne It has been tried on occasions but abandoned in favour of the simpler serological tests It has been strongly supported by Maclagan (1947) and by Althausen (1948) Maclagan uses the galactose index which is the sum of the four blood galactose values obtained at ½ 1 1½ and 2 hours after the oral administration of 40 grams of the sugar It cannot be performed in the presence of nausea or vomiting Further it has the disadvantage of giving abnormal values in obstructive jaundice present for more than 3 weeks in febrile or cachectic patients and with recurrent attacks of obstruction To overcome some of these disadvantages the intravenous method has been used Althausen claims that the majority of cases of obstructive jaundice showed values for the blood galactose of less than 20 milligrams per cent, 75 minutes after injection of the test dose Further the majority of cases of parenchymatous jaundice showed values greatly in excess of 20 milligrams per cent In his review of nearly 200 cases of jaundice there are still

Contra indications

These may be summarized as follows an uncooperative patient—full co operation is essential unless the subcostal route can be used presence of a liver abscess amoebiasis or hydatid disease severe anaemia—particular care should be taken before attempting biopsy in cases of aplastic or hypoplastic anaemia or severe bleeds will follow haemorrhagic states particularly *if the response to* treatment is doubtful presence of gross pulmonary disease with dyspnoea—again the subcostal route may be possible here

In summary liver biopsy has become a useful diagnostic and experimental procedure With care and experience the hazard is minimized but it should not be undertaken lightly by the inexperienced In Melbourne practice on cadaver material has been insisted upon as a preliminary in those learning the technique

TESTS OF LIVER FUNCTION

In the past 12 years there has been a steady growth in the number and variety of tests of liver function Although these tests are included under the generic name Function Tests in certain cases this is a misnomer and what is being observed is the biochemical changes occurring during the course of liver disease Many tests that have been described are complex and difficult to carry out thus limiting their use to the experimental laboratory Again some have been found of small clinical *value and have not stood the test of time*

It is generally agreed that tests of liver function are not to be regarded as a short cut to diagnosis and that they can never replace the careful history and examination When taken in conjunction with the latter they can prove of real value The most use ful tests and the number required will be discussed after a classification has been given

Tests associated with pigment metabolism (1) bilirubin content of blood van den Bergh s test icterus index (2) bilirubin tolerance test (3) urobilinogen levels in urine and faeces (4) bile components in the urine

Tests associated with carbohydrate metabolism (1) galactose tolerance test (2) glucose tolerance test (3) laevulose tolerance test

Tests associated with lipid metabolism (1) cholesterol content of blood (2) ratio of cholesterol esters to total cholesterol

Tests associated with protein metabolism (1) total serum proteins and albumin—globulin ratio (2) amino acid tolerance (3) blood prothrombin level and its response to vitamin K (4) flocculation and precipitation tests (a) Takata Ara (b) colloidal gold reaction *(c) cephalin cholesterol flocculation (d) thymol* turbidity and *flocculation (e) colloidal red test*

Tests based on conjugation or excretion of foreign substances by the liver (1) hippuric acid synthesis (2) bromsulphalein excretion

Unclassified level of serum alkaline phosphatase

Van den Bergh reaction

The qualitative test can no longer be accepted as an indication of the underlying pathological change in the liver For years after its introduction great stress was laid on direct and indirect reactions as pointing to obstructive and hepato cellular jaundice respectively This concept has been strongly challenged by Bockus

presence of inversion of the albumin-globulin ratio is almost diagnostic of hepatocellular jaundice The only exception is where obstruction has been present for so long that biliary cirrhosis has supervened

In infective hepatitis the presence of this inversion is a warning that complications may ensue The persistence of this inversion points to the likelihood of the disease persisting in a chronic form In a series of 14 cases of chronic hepatitis studied in Melbourne the return to normal of this ratio was always followed by definite clinical improvement As long as inversion remained the patient was always in danger and in the 7 deaths in this series the ratio was inverted in all Higgins and others (1944) have drawn attention to its usefulness in assessing prognosis Similar results may be seen in cirrhosis of the liver Post and Patek (1942) claim the level of the serum albumin is the most important diagnostic fact As long as this remains low response to therapy is inadequate

Amino acid tolerance

The level of blood amino acids only arises in extreme degrees of liver dysfunction Estimations devised to show the response to amino acids given orally or intravenously have failed mainly due to technical difficulties Dent (1946) introduced a moderately simple method of demonstrating tyrosine and leucine in the urine — this again is only an index of extreme liver failure

Blood prothrombin level and its response to vitamin K

Theoretically this should be an ideal method of distinguishing hepatocellular from obstructive jaundice and it should also be a sensitive index of disturbed liver function Lord and Andrus (1941) claimed that if a satisfactory rise in prothrombin occurred after giving vitamin K intramuscularly the jaundice was obstructive in nature This is not entirely true since not all cases of hepatocellular jaundice show a lowered prothrombin value also milder cases of infective hepatitis may show a satisfactory response to vitamin K parenterally Althausen claims that 96 per cent of cases of hepatocellular jaundice failed to show a rise of 20 per cent or more following vitamin K therapy In the obstructive group he found that 91 per cent gave a satisfactory rise

In Melbourne our experience has not quite agre d with the above mentioned workers Certainly in severe liver disease it has been impossible to raise the prothrombin level by giving vitamin K in large doses To this end it may be considered as an index of liver function One of the greatest worries has been on the technical side in obtaining standard results For this reason it is not recommended for differentiating the types of jaundice but as it is usually done before biopsy or laparotomy it may give some additional information

Cephalin cholesterol flocculation

This is the most widely used of a number of serological tests It was originally described by Hanger (1939) and has largely replaced the Takata Ara and colloidal gold tests It has proved more useful than the latter two in the differentiation of the obstructive from hepatocellular jaundice It depends on the alteration of a physical state which can be observed and as Kabat and others (1943) have shown is associated with an alteration in the relative levels of the serum proteins Probably

discrepancies present in the results particularly where obstruction had been present for any length of time or was recurrent

Glucose and laevulose tolerance

No general agreement has been reached as to the most satisfactory method of performing these and the results have varied in the hands of different investigators They may be regarded almost as museum pieces in the realm of liver function tests

Total blood cholesterol—ratio of cholesterol esters

The use of this estimation originated in Germany but it has been developed and used extensively in the United States of America Normally the serum cholesterol content is between 140 and 200 milligrams per 100 millilitres Of this total between 50 and 70 per cent is in the esterified form In obstructive jaundice an increase in total cholesterol is a fairly constant biochemical feature When this rise does not occur in jaundiced patients it is usually due to parenchymatous liver disease At the same time in obstructive jaundice the rise of esterified cholesterol is proportional to total cholesterol—so the ratio remains constant If there is liver damage the rise in cholesterol esters does not occur

In hepatocellular jaundice the total cholesterol does not rise and may even fall Even more striking than this is the decrease of the esterified portion The decrease in esters is approximately the degree of liver cell damage—in severe grades esterified cholesterol may almost disappear from the blood As recovery takes place the rise in cholesterol esters roughly parallels this

In 623 cases of infective hepatitis studied in Germany in 1947–48 Gardner and others (1950) found a drop in cholesterol esters in the first weeks with a return to normal during convalescence None showed hypercholesterolaemia and only three had a blood cholesterol level below 100 milligrams per cent

Unfortunately blood cholesterol is labile and a sudden drop may be seen in hyperthyroidism and infections Similarly the esters are even more labile and may drop quite sharply with a slight degree of liver cell damage following obstructive jaundice This detracts from the reliability of the test in differentiating obstructive from hepatocellular jaundice Further the alterations in blood cholesterol occurring with infection also make the test unreliable where mechanical obstruction has been present for any time Finally elevation of the blood cholesterol is well known in hypothyroidism the nephrotic syndrome and pregnancy

Epstein and Greenspan (1936) found positive evidence of hepatocellular jaundice by this means in 75 of 111 cases of hepatitis In 11 cases of this series the value was above 300 milligrams In their series of 105 cases of obstructive jaundice 82 showed definite elevation Shay and Siplet (1948) claim very good approximation to the correct diagnosis by the use of this test Its main use seems to be in estimating the degree of hepatic damage and in this manner a very good idea may be obtained of the amount of recovery that is occurring This particularly applies to cholesterol esters and if their percentage remains low the outlook is usually poor

Total serum proteins—albumin-globulin ratio

This has proved to be one of the most useful tests of liver function It is helpful in diagnosis and particularly helpful in assessing prognosis In jaundice the

presence of inversion of the albumin–globulin ratio is almost diagnostic of hepatocellular jaundice. The only exception is where obstruction has been present for so long that biliary cirrhosis has supervened.

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this follows a rise in the globulin fraction A strongly *positive reaction is nearly* always indicative of parenchymatous liver disease but this has been observed in glandular fever Sometimes cases of infective hepatitis may fail to show any *flocculation or it may appear late in the* course of the disease At other times only a weak positive reaction may be obtained (usually designated + + in 48 hours whereas a strong positive is + + + +) A word of warning is necessary that most cases of obstructive jaundice where cholangitis has occurred will show a weak positive reaction

In cirrhosis of the liver the presence of *a strong positive flocculation* means the process is still active In the inactive form flocculation is usually negative This has been checked with biopsy material The sensitivity of this has been challenged by those favouring the thymol turbidity test of Maclagan Neefe (1946) has shown that the thymol turbidity may give positive evidence of residual liver damage after the other tests have become negative

In summary in Melbourne it has been found most useful in detecting parenchymatous liver disease provided the limitations mentioned above are remembered *Occasionally these have been forgotten and errors have occurred but this is not the* fault of a very useful test

Thymol turbidity test

First devised by Maclagan in 1944 it is one of the most popular tests of liver *function Most series published show that it is a more sensitive index of liver* cell damage than the other flocculation tests It has the added advantage of giving an answer within the hour instead of the 48 hour period necessary in the cephalin cholesterol flocculation Further the solutions required are more easily prepared

From a study comparing cephalin flocculation and thymol turbidity Watson and Rappaport (1945) concluded that the underlying mechanism was different in the two Maclagan has stated that the presence of phospholipids is essential for the thymol reaction *and these are associated mainly with the β globulin fractions* Nevertheless experimental work appears to show that it is the γ globulin fraction that is important for the reaction and the β globulin acts merely by contributing phoshholipid

Shay and Siplet (1948) carried out cephalin flocculation colloidal gold and thymol turbidity on the sera of 76 patients with symptoms referable to the alimentary tract but without any evidence of liver disease

The cephalin flocculation was positive in 7 (9 2 per cent) colloidal gold in 38 *(50 per cent) while the thymol turbidity was normal in all)* Numerous other workers have produced similar results The normal limits as originally described by Maclagan (1944) were 0–4 units This has been criticized by Neefe (1946) and Mateer and others (1943) who consider values above *2 units are abnormal* As Maclagan has subsequently pointed out if values below 4 units are accepted the number of false positives will increase He has found extrahepatic disease to give values between 2 and 4 units If this is used as a method of screening in the presence of an outbreak of hepatitis values over 2 units are suggestive of liver involvement

The only criticism is this very specificity At times it has been found to be negative in cirrhosis particularly on occasions where jaundice was present and

subsequently shown to be hepatocellular in type. Much better results are obtained if it is used in conjunction with the cephalin flocculation (Neefe and others 1950) There is also evidence from the United States of America that the thymol turbidity is less frequently positive in homologous serum jaundice than in infective hepatitis, whereas the cephalin flocculation is positive in both

Further information may be obtained by allowing the tube in which thymol turbidity has been estimated to stand overnight and recording the degree of flocculation This gives the thymol flocculation as described by Neefe (1946) and Maclagan (1947) Some difficulty may be experienced in grading the degree of flocculation and Maclagan recommends that this be related to the turbidity reading Incomplete flocculation was designated "1" and absent flocculation as "0" or negative This addition to the thymol turbidity makes for more complete results and is easy to carry out. Maclagan has shown that thymol flocculation may be more useful in aiding diagnosis than the thymol turbidity

Other flocculation tests

Mention has already been made of the Takata Ara and colloidal gold tests. Other tests include cadmium sulphate (Wunderly and Wuhrmann 1945) sharlach red (Maizels 1946) zinc sulphate (Kunkel 1947) colloidal benzoin and shellac (Fischer and Wiltner 1949) Of all these the colloidal red reaction (Ducci, 1950) seems to be the most effective and the simplest to perform Its specificity seems to approximate to that of the colloidal gold reaction It gives frequent positive reactions in non hepatic conditions but in dealing with jaundiced patients it was positive in 81 per cent of cases of hepatocellular jaundice In obstructive jaundice negative results were obtained in 83 per cent of cases This series comprised 329 patients with jaundice (Ducci 1950) Recent results from Germany show that it has no advantages over the use of cephalin flocculation and thymol turbidity in combination (Neefe and others 1950)

Hippuric acid synthesis

This test enjoyed a long vogue of popularity which began to wane in 1946 and has continued to do so It has the disadvantage of being somewhat cumbersome as several specimens have to be collected If the intravenous modification is used there is the trouble of an intravenous injection as well. In Melbourne it has now been abandoned as a reliable test of liver function Its fate was largely sealed by the advent of liver biopsy when difficulty was found in correlating normal histology with grossly abnormal results from this estimation Sherlock has shown that in the absence of liver disease abnormal values may be obtained in renal disease anaemia diabetes pneumonia and malignant disease not involving the liver In a further study she found very little relation between an impaired hippuric acid and the appearance of the liver in biopsy material For these reasons its use should be abandoned particularly in small laboratories where it is time-consuming out of all proportion to its value in diagnosis and prognosis

Bromsulphalein excretion

This suffers from two defects It is not feasible to use it in the presence of obstructive jaundice as the dye is excreted in the bile and secondly it requires an

intravenous injection and subsequent collection of specimens of blood In a recent study Havens and others (1950) have shown some rough correlation between the level of serum bilirubin (above normal limits) and the degree of dye retention

The main value of this procedure is in assessing hepatic dysfunction without obstructive jaundice particularly in diffuse lesions as cirrhosis Here the usual method is to give 5 milligrams bromsulphalein per kilogram body weight and to take a venous blood sample at the end of 45 minutes when all the dye should have disappeared from the blood (Mateer and others 1943) Used in this way it is a reliable indicator of the state of the liver in the absence of jaundice It should be performed in the fasting state as Havens has shown an increased capacity to clear the blood of dye within 60 to 90 minutes after meals This finding was common to normal controls and patients with liver disease

A more recent use of this dye excretion has been found in the screening of patients with haematemesis and melaena Zamcheck and others (1950) claim uncomplicated bleeding peptic ulcers give normal results whereas patients with cirrhosis show a high and continued dye retention Other liver diseases such as fatty changes metastic carcinoma and cholangitis did not show such clear cut and definite results

It seems that its main use is in suspected liver disease without jaundice where simpler procedures have given negative or equivocal results

Serum alkaline phosphatase

It is still controversial why the blood phosphatase levels are raised in liver disease but this does not detract from the value of this estimation in the differentiation of the types of jaundice Naturally bone disease has to be excluded first—Sharnoff and others (1942) have stated that in the absence of skeletal disease alkaline phosphatase levels depend initially on the degree of damage to liver cells Attempts have been made to show that this substance is liberated from necrotic liver cells but this does not entirely explain the degree of elevation that may be found It appears that this enzyme is excreted in the bile There are two methods of estimation which give different results for normal values—most British workers use the method of King and Armstrong (normal 5–13 units) whereas Americans seem to prefer the modified Bodansky technique (normal 2–9 units)

As in all liver function tests a solitary result is without meaning When the level of alkaline phosphatase is taken in conjunction with other tests it will be found to be most useful The highest values are obtained in obstructive jaundice usually due to carcinoma but quite often slight to moderate elevation may be seen in infective hepatitis Sherlock used a level of 30 units as an arbitrary dividing line and this has been found most valuable in clinical applications Maclagan in reviewing the use of this estimation in 200 cases of jaundice suggests that this may be too low His contention is that equivocal results occur in the 30–35 range In his series all cases with phosphatase levels above 40 units were obstructive and all below 15 units non obstructive He rightly points to the higher levels obtained in chronic as opposed to acute hepatitis Occasionally cases of chronic hepatitis may be found to have levels of alkaline phosphatase over 60 units particularly in the cholangiolitic type of Watson and Hoffbauer (1946)

Despite these variations for ordinary clinical practice 30 units is the best dividing line In my experience jaundice with a normal or only slightly raised level of phosphatase is always hepatocellular On two occasions this reading has been ignored and laparotomy performed for a progressive jaundice On both occasions cirrhosis was found to be the cause

In cases of hepatomegaly the presence of a high value for alkaline phosphatase with normal values for other liver function tests should make one think of secondary carcinomatous involvement of the liver Recently three cases have been seen where this was confirmed at laparotomy or by biopsy Various theories have been advanced to explain this phenomenon including partial obstruction to the biliary tree but not of sufficient degree to produce jaundice At the present it remains unexplained

Recent tests

Under this heading two procedures still in the experimental stage may be mentioned The first is the use of radioactive phosphorus in assessing the rate of phospholipid formation in the liver (Cayer and Cornatzer 1950) It is suggested that an increase in phospholipid turnover following a single large dose of choline may indicate fatty change in the liver cells

The second is the use of serum globulin fractions These values are now being obtained by chemical methods Spellberg and others (1950) have recently shown that elevation of the γ globulin was the most frequently encountered abnormal test for disturbed liver function This elevation occurred earlier and persisted longer than did abnormalities in other tests of liver function They confirmed Martin s (1946) findings that the elevation of the α globulin concentration seemed to be associated with a tendency for the hepatitis to become chronic or with more severe liver involvement These tests are still too difficult for routine laboratory use

The most informative and useful tests in the diagnosis of jaundice are estimation of serum bilirubin and urinary urobilinogen cephalin cholesterol flocculation and thymol turbidity and flocculation serum alkaline phosphatase and estimation of total serum protein and the albumin–globulin ratio

There is no evidence that the more elaborate tests will give any more information than can be obtained from the above This selection also has the advantage of only requiring 10 millilitres of blood and a specimen of urine from the patient and does not make too great a demand on laboratory facilities In dealing with hepatomegaly without jaundice disappointing results may be obtained especially with cases of inactive cirrhosis Even bromsulphthalein excretion will not help beyond pointing out some liver dysfunction

In conclusion liver function tests when taken in conjunction with a clinical history and examination are of definite value in elucidating the problem of jaundice They must never be expected to replace clinical methods nor must single tests be done

REFERENCES

Althausen T L (1948) *Amer J Med* 4 208
Bjorneboe M Iversen P and Keiding R (1949) *Acta med scand* 135/5 303
Bockus H L (1946) *Gastroenterology* 3 70
Cayer D and Cornatzer W E (1950) *Ibid* 14 1

Cogswell R C Schiff L Safdi S A Richfield D F Kumpe C W and Gall E A (1949) *J Amer med Ass* **140** 385
Corkhill A B Pollock D J and Smith G E (1946) *Med J Aust* **1** 617
Dameshek W and Singer K (1941) *Arch intern Med* **67** 259
Dent C E (1946) *Lancet* **2** 637
Ducci H (1950) *Gastroenterology* **14** 20
Epstein E Z and Greenspan E B (1936) *Arch intern Med* **58** 860
Fischer A and Wiltner W (1949) *Acta med scand* **134/5** 371
Gardner H I Swift W E Jun Modica M Levintow L and Knowlton M (1950) *Amer J Med* **8** 584
Gillman T and Gillman J (1945) *S Afr J med Sci* **10** 53
Gray C H (1947) *Quart J Med* **16** 135
Hanger F M (1939) *J clin Invest* **18** 261
Havens W P Jun Miller W N Swift W E Jun Gardner H T and Knowlton M (1950) *Amer J Med* **8** 591
Higgins G O Brien J R P Stewart A and Witts L J (1944) *Brit med J* **1** 211
Iversen P and Roholm K (1939) *Acta med scand* **102** 1
Kabat E A Hanger F M Moore D H and Landow H (1943) *J clin Invest* **22** 563
King W E and Downie E (1948) *Quart J Med* **17** 67 247
— and Perry J W (1948) *Med J Aust* **1** 697
— Motteram R Weiden S and Wood I J (1949) *Ibid* **2** 532
Krarup N B and Roholm K (1941) *Klin Wschr* **20** 193
Kunkel H G (1947) *Proc Soc Exp Biol N Y* **66** 217
Lord J W Jun and Andrus W de W (1941) *Arch intern Med* **68** 199
Lucatello L (1895) *Lav Congr Med interna* **6** 327
Maclagan N F (1944) *Brit med J* **ii** 363
— (1944) *Brit J exper Path* **25** 234
— (1947) *Brit med J* **2** 197
— (1948) *Ibid* **2** 892
McMaster P D and Rous P (1921) *J exp Med* **33** 731
McNee J W (1923) *Quart J Med* **16** 390
Maizels M (1946) *Lancet* **2** 451
Martin N H (1946) *Brit J Exp Path* **27** 363
Mateer J R Baltz J I Marion D F and MacMillan J M (1943) *J Amer med Ass* **121** 723
Meulengracht E (1947) *Quart J Med* **16** 83
Mollison P L (1948) *Lancet* **1** 513
Neefe J R (1946) *Gastroenterology* **7** 1
— Gambescia J M Gardner H T and Knowlton M (1950) *Amer J Med* **8** 600
Parsons P J Garlick H W and Motteram R (1948) *Roy Melbourne Hosp Clin Repts Centenary Vol* 236
Post J and Patek A J (1942) *Arch intern Med* **69** 67
Readinger H M Swift W E Jun Gardner H I and Sheedy J A (1950) *Amer J Med* **8** 611
Rich A R (1930) *Bull Johns Hopk Hosp* **47** 338
Roberts W M (1933) *Brit med J* **1** 734
Scadding J G and Sherlock S P V (1948) *Thorax* **III** 79
Sharnoff J G Lisa J R and Riedel P A (1942) *Arch Path* **33** 460
Shay H and Siplet H (1948) *Amer J Med* **4** 215
Sherlock S P V (1945) *Lancet* **2** 397
— (1946) *J Path Bact* **58** 523
Spellberg M A Cohn C Wolfson W O and Shore C (1950) *Gastroenterology* **14** 11
Terry R (1949) *Brit med J* **1** 657
Topp J H Lindert M F C and Murphy F D (1948) *Arch intern Med* **81** 832
Van Beek C and Haex A J (1943) *Acta med scand* **113** 125
Volwiler W and Jones C M (1947) *New Eng J Med* **237** 651
Watson C J (1937) *Arch intern Med* **59** 196
— Hoffbauer F W (1946) *Ann intern Med* **25** 195

Watson C J and Rappaport E. M (1945) *J Lab clin Med* 30 983
Weisbrod M L. Schiff L. Gall E A. Cleveland F P and Berman J R (1950) *Gastroenterology* 14 56
Whipple A O (1945) "Diseases of the Pancreas *In Nelson s Loose Leaf Medicine* Vol V p 531 New York Nelson
Wunderly C and Wuhrmann F (1945) *Schwei Med Wchnschr* 75 1128
Zamcheck N Chalmers T C White F W and Davidson C S (1950) *Gastroenterology* 14 343

CHAPTER 31

ACUTE VIRUS HEPATITIS AND HEPATIC CIRRHOSIS

SECTION I

ACUTE "VIRUS" HEPATITIS

SHEILA SHERLOCK

ACUTE hepatitis is a diffuse inflammation of the liver parenchyma with or without jaundice and probably caused by a virus infection Two main groups are recognized acute infective hepatitis and homologous serum hepatitis Hepatitis due to suppurative lesions of the liver to amoebae and hepatitis associated with other virus diseases such as infectious mononucleosis will not be considered

AETIOLOGY AND EPIDEMIOLOGY

An epidemic type of jaundice has been recognized for centuries the first known reference being ascribed to Hippocrates The earliest record of the disease in Western Europe is mentioned by Ford (1943) as occurring in a letter written in A D 751 by Pope Zacharias to St Boniface Archbishop of Mainz Since then medical literature has contained numerous accounts of epidemics which increased in frequency in war time Epidemic jaundice was a problem in the Franco Prussian War the American Civil War and World War I World War II was no exception and huge epidemics occurred particularly in the Middle East and Italy Between the wars the disease manifested itself by sporadic cases and minor epidemics The historical aspects are well described by Lucké (1944) and Gardner (1950)

The exact nature of the disease has only been determined in the last decade This delay may be attributed to two main factors first the characteristic innocent nature of the illness so that post mortem material did not become available and secondly to a misconception about its pathogenesis This latter arose from a post mortem observation by Virchow (1865) on a patient suffering from epidemic jaundice who was accidentally killed Duodenitis was found which had caused catarrh at the lower end of the main bile duct with swelling of the mucosa and obstruction to bile outflow and the condition was termed catarrhal jaundice Evidence against this obstructive hypothesis of epidemic jaundice accumulated slowly The occasional fatal case showed a liver which was the site of acute parenchymal inflammation—an *acute yellow atrophy in miniature* (Eppinger 1937) Intubation of the duodenum with study of the aspirated contents failed to confirm the diagnosis of duodenitis Biochemical tests of liver function gave results indicating not biliary obstruction but diffuse liver cell damage Eventually the introduction of a safe method of aspiration liver biopsy enabled the hepatic histology to be studied in all stages of the disease The hepatic lesion was in fact shown to be an *acute inflammation* (Roholm and Iversen 1939 Dible McMichael

and Sherlock 1943) The concept of an acute epidemic catarrhal jaundice has now been generally abandoned

Attempts to discover the cause and mode of spread of epidemic jaundice were hindered by the failure to find an animal susceptible to the disease Attempts have been made to transmit the disease to every conceivable type of animal and although from time to time reports of success with pies canaries and the chick embryo have appeared the results have yet to be confirmed (MacCallum 1944 Havens 1948 Henle and others 1950a) There are no susceptible experimental animals and research has proceeded only with the aid of human volunteers The number in any one experiment therefore is of necessity small and the results have to be interpreted with caution

Epidemic jaundice is now known to be due to a hepato-tropic filtrable infectious agent which is believed to be a virus At least two agents are recognized one causing infective hepatitis and the other homologous serum jaundice The main differences between the two diseases lie in the incubation period and mode of transmission Infective hepatitis produces the disease 2–6 weeks after oral or parenteral exposure to the infecting agent homologous serum jaundice characteristically develops 2-6 months after the occurrence of an opportunity for parenteral entry of the virus Any hepatitis syndrome occurring up to 6 months after exposure may be of viral origin and represent homologous serum hepatitis (Neefe 1949)

The virus of infective hepatitis is present in the blood and faeces of sufferers during the pre icteric and icteric phases of the disease It disappears during con valescence *It is uncertain whether the agent is found in nasopharyngeal droplets* or urine The commonest mode of spread is by faecal contamination anything subject to direct or indirect contact with faeces is a potential means of transmission Most sporadic cases follow person to person contact Explosive water borne and food borne epidemics are described An excellent account of such an epidemic is given by Neefe and Stokes (1945) in which faecal contamination of the water supply of a children s camp resulted in 350 cases of infective hepatitis among 572 campers It is easy to understand how the insanitary conditions occurring in war time have led to recurring outbreaks of the disease

Homologous serum hepatitis results from the parenteral introduction of blood and blood products contaminated by the virus The possible existence of such a mode of spread of epidemic jaundice was realized as long ago as 1885 by Lurman He observed jaundice in 191 of 1 289 workmen vaccinated against smallpox whereas 500 men vaccinated at the same time but with a different lymph failed to acquire the disease Later accounts appeared of epidemics of jaundice in children receiving convalescent serum as a prophylactic against measles (Propert 1938) or mumps (Beeson Chesney and McFarlan 1943) The occurrence of over 50 000 cases of acute hepatitis in the United States Forces receiving prophylactic yellow fever vaccine was final proof of this hazard of serum inoculations Clinically the disease was almost identical with infective hepatitis It did not recur when a different vehicle was used for the vaccine Another mode of spread of homologous serum jaundice is by contamination of instruments used for parenteral therapy An excellent example of this is the periodic epidemics of jaundice occurring in venereal clinics among patients receiving arsenic injections The resultant jaundice occurs about 10 weeks after the first attendance at the clinic The

CHAPTER 31

ACUTE VIRUS HEPATITIS AND HEPATIC CIRRHOSIS

SECTION I

ACUTE "VIRUS" HEPATITIS

SHEILA SHERLOCK

ACUTE hepatitis is a diffuse inflammation of the liver parenchyma with or without jaundice and probably caused by a virus infection Two main groups are recognized acute infective hepatitis and homologous serum hepatitis Hepatitis due to suppurative lesions of the liver to amoebae and hepatitis associated with other virus diseases such as infectious mononucleosis will not be considered

AETIOLOGY AND EPIDEMIOLOGY

An epidemic type of jaundice has been recognized for centuries the first known reference being ascribed to Hippocrates The earliest record of the disease in Western Europe is mentioned by Ford (1943) as occurring in a letter written in A D 751 by Pope Zacharias to St Boniface Archbishop of Mainz Since then medical literature has contained numerous accounts of epidemics which increased in frequency in war time Epidemic jaundice was a problem in the Franco Prussian War the American Civil War and World War I World War II was no exception and huge epidemics occurred particularly in the Middle East and Italy Between the wars the disease manifested itself by sporadic cases and minor epidemics The historical aspects are well described by Lucke (1944) and Gardner (1950)

The exact nature of the disease has only been determined in the last decade This delay may be attributed to two main factors first the characteristic innocent nature of the illness so that post mortem material did not become available and secondly to a misconception about its pathogenesis This latter arose from a post mortem observation by Virchow (1865) on a patient suffering from epidemic jaundice who was accidentally killed Duodenitis was found which had caused catarrh at the lower end of the main bile duct with swelling of the mucosa and obstruction to bile outflow and the condition was termed catarrhal jaundice Evidence against this obstructive hypothesis of epidemic jaundice accumulated slowly The occasional fatal case showed a liver which was the site of acute parenchymal inflammation—an acute yellow atrophy in miniature (Eppinger 1937) Intubation of the duodenum with study of the aspirated contents failed to confirm the diagnosis of duodenitis Biochemical tests of liver function gave results indicating not biliary obstruction but diffuse liver cell damage Eventually the introduction of a safe method of aspiration liver biopsy enabled the hepatic histology to be studied in all stages of the disease The hepatic lesion was in fact shown to be an acute inflammation (Roholm and Iversen 1939 Dible McMichael

are identical The aetiological viruses are both filtrable and resistant to a temperature of 50 C for 30 minutes The main difference lies in the incubation period of the two diseases Aycock and Oren (1947) believe that homologous serum jaundice may merely represent the artificial dissemination of the naturally occurring disease Parenteral transmission involves not only inoculation of virus but also of serum Administration of any virus with an immune serum is known to prolong the incubation period However there is no cross immunity between the two conditions and a volunteer recovering from infective hepatitis can be infected with the virus of homologous serum jaundice and *vice versa* An attack of either infective hepatitis or homologous serum jaundice however does guard against a further attack of the same disease (Neefe Gellis and Stokes 1946 Havens 1947) The exact duration of this homologous immunity is unknown The differences between the two viruses as regards mode of infection and the nature of the infective material have already been discussed These are summarized in Table I

TABLE I

THE EPIDEMIOLOGY OF ACUTE INFECTIVE HEPATITIS AND SERUM HEPATITIS

	Infective hepatitis	Serum hepatitis
Incubation period		
Weeks	2-6	8 24
Mode of infection		
Faeces	+	—
Urine	? —	? —
Nasopharyngeal droplets	? —	? —
Blood	? —	+
Oral or parenteral	Oral or parenteral	Parenteral
Period infective		
Incubation	? —	+
Pre icteric	+	+
Icteric	+	+
Convalescent	—	? —

PATHOLOGY OF ACUTE VIRUS HEPATITIS

There are no pathological differences in the organs from sufferers from either homologous serum hepatitis or infective hepatitis

Hepatic changes

In the fatal case the liver is characteristically reduced in size being smallest in those patients who die the soonest The organ appears flaccid and shrunken The left lobe is often disproportionately atrophied in relation to the right This has been attributed to nutritional factors and compared to the massive dietetic necrosis in rats which also involves the left lobe more than the right (Himsworth and Glynn 1944) The left lobe obtains its portal blood supply mainly from the

clinical features do not resemble those ascribed to syphilis or arsenic toxicity Moreover it can be prevented by a scrupulous technique of syringe sterilization so that individual syringes are used for each patient (Salaman King Williams and Nicol 1944) It can be shown that the blood of sufferers from this arseno therapy jaundice contains an agent which will transmit jaundice to healthy volunteers (MacCallum 1945) As little as 0 01 millilitre of contaminated serum is sufficient to transmit the disease and this can easily remain inside a dirty syringe or needle after inefficient cleansing Later other epidemics of jaundice were reported from clinics where parenteral techniques are used for instance diabetic clinics rheumatic clinics and sanatoria Any procedure involving the parenteral intro duction of blood or its products involves the hazard of homologous serum jaundice This includes intravenous intramuscular subcutaneous and intra cutaneous injections and punctures It results from contaminated serum remain ing in imperfectly sterilized syringes needles or stilettes

Plasma infusion therapy is a particularly common method of spread of serum hepatitis The plasma in the blood bank is usually pooled and each bottle contains plasma from many donors The chance of the plasma from one of the donors harbouring the virus is great and the incidence of jaundice among patients receiving plasma from pools obtained from more than 300 donors is 11 9 per cent For small pools (less than 10 donors) and whole blood the incidence is about 1 per cent (LeHane Kwantes Upward and Thompson 1949) Transfusion of whole blood of course is much less likely to cause jaundice but this also is not entirely without risk Biting insects also cannot be excluded as a possible mode of transmission (Neefe 1949) The possible medico legal implications of blood transmitted hepatitis is illustrated by the unfortunate experience of a certain Italian physician

> After a trial of more than one month and a verdict elaborated in 16 hours the physician of Varese who had been accused of disseminating by his imperfect technique the epidemic of syringe hepatitis was sentenced to serve 5 years in prison to dis continue practice for 2 additional years and to compensate the families of the victims of whom 12 had died and an additional 100 were infected This physician gave no less than 50 intravenous injections of a tonic to his patients every day (1948)

Homologous serum hepatitis is spread only by parenteral inoculation of infected blood The faeces of the sufferer are not infective Urine and naso pharyngeal droplets also probably do not contain the virus This explains the absence of contact cases from the huge epidemics of serum jaundice described above The disease differs from the infectious hepatitis in that the blood of the sufferer is infective throughout the incubation period as well as in the immediate pre icteric or early icteric stages Blood during convalescence probably does not contain the virus (Havens 1948)

There is much discussion concerning differences between the causative agents of infective hepatitis and those of homologous serum jaundice Certainly epidemics of both types tend to occur at the same time a point well illustrated by the epidemics of 1943 in North Africa and later in Italy The two diseases have almost identical clinical courses and the resulting pathological changes in all the organs

acute hepatitis surviving liver cells retain their complement of glycogen well Fatty change in the liver cells might also be expected but is conspicuous by its absence Haemosiderosis does not occur The essential reticular framework of the liver is maintained surprisingly well although where there is much centilobular loss of liver cells there is condensation of reticulin The same condensation may also be noted The necrosing liver cells may show bile staining and the aggregation of bile pigment to form thrombi which are found at the centres of the lobules These are rarely as conspicuous as those found in obstructive surgical jaundice Bile-duct proliferation may occur in the portal tract but again is less than that seen in obstructive jaundice

These hepatic histological changes are found even before the development of jaundice and at this time are often as severe as those seen in the icteric phase

The course of the hepatic changes

Recovery is by far the commonest pathological sequence and eventual full anatomical restitution of the liver occurs in about 99 8 per cent of patients Once instituted the recovery is very rapid providing an example of the tremendous regenerative capacity of the liver

A striking feature of the acute stage is the remarkable preservation of the reticulin framework of the liver lobule even in the midst of extreme disorganization of the liver cells It seems probable that this framework of reticulin provides a scaffolding in which the lobule is reconstructed when the liver cells regenerate The lobular pattern is restituted regeneration proceeding from without inwards the cells adjoining the central vein being the last to recover Cellularity disappears gradually from the portal tracts and some new portal connective tissue can often be found many months after clinical recovery from acute hepatitis This residual portal tract scarring must not be confused with the hepatic cirrhosis that sometimes develops after hepatitis Other histological features of the recovery phase are increased reticulo endothelial activity throughout the lobule apparently a scavenger phenomena and a slight increase in stainable fat possibly due to a temporary metabolic inadequacy of the newly formed liver cells

Acute hepatic necrosis (fulminant hepatitis)

Centilobular hepatic cell necrosis is a constant finding in acute virus hepatitis Occasionally however the liver cell damage is so extensive that the lesion corresponds to the acute yellow atrophy of older writers This diagnosis is difficult to make on post mortem studies of liver as the organ atrophies particularly rapidly after death and this is very marked in the presence of acute necrosis (Van Beek and Haex 1943) In the few available biopsies the liver lobular structure can no longer be identified and hepatic cell necrosis is widespread Even in those severe cases the reticular framework may be preserved intact

Subacute hepatic necrosis

Fatal cases that survive longer than about two weeks show a different histological picture Necrosis of liver cells proceeds side by side with hepatic cellular regeneration Macroscopically therefore the liver is enlarged with nodules of regeneration of varying sizes seen both on the surface and in section Histologically wide

stomach and spleen and receives a less abundant supply of amino acids than the right which receives blood from the absorptive areas of the small *intestine*

In patients surviving more than about two weeks areas of nodular regeneration may be seen The cut surface shows an exaggerated nutmeg appearance with red areas of necrosis and haemorrhage alternating with yellow patches of necrotic liver cells The naked eye appearance of the liver does not indicate the extent of the underlying lesion The gross hepatic changes in fatal hepatitis have been well described by Lucke (1944) and Lucke and Mallory (1946)

The macroscopic changes found *in the more ordinary non fatal case can be* assumed to be a lesser degree of those described above

The sequence of hepatic histological changes have been built up as a result of aspiration liver biopsy studies (Roholm and Iversen 1939 Axenfeld and Brass

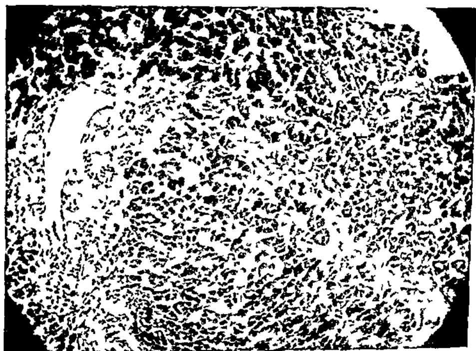


FIG 249 —Acute infective hepatitis The lobular pattern is preserved There is centilobular liver cell necrosis and increased round cells in the portal tracts B st s carmine stain × 112 5

1942 Dible and others 1943) The essential lesion is an acute inflammation of the entire liver The histological picture is one of hepatic cell necrosis and autolysis associated with leucocytic and histiocytic reaction and infiltration The centres of the lobule show the first of these changes most markedly and the portal tracts the greatest cellular infiltration (*Fig 249) The hepatic sinusoids show general* hyperplasia of their endothelial cells and there are occasional focal accumulations of these cells Polymorph leucocytes and eosinophils may also be seen in the lumina of the *sinusoids* Glycogen disappears early in experimental liver damage but in

areas of devastation in which only haemorrhage and a few proliferating bile ducts are seen alternate with nodules of regenerating liver cells (Fig. 250) The hepatic lobular structure is now totally disorganized and new reticular bands are found in the areas of liver cell disappearance If recovery occurs anatomical restitution of the liver lobule is no longer possible and a hepatic cirrhosis is inevitable

Hepatic cirrhosis follows a very severe hepatitis in which the reticular framework of the liver lobule has been disorganized There is condensation of reticulin where the liver cells have disappeared together with formation of much new connective tissue Liver cells regenerate in a nodular fashion and the normal lobular pattern is no longer maintained

The activity of the hepatic lesion is very variable there being all gradations from subacute necrosis to a cirrhosis in which acellular fibrous bands are conspicuous and liver cell damage is minimal (Fig 251) This latter is by far the commonest histological picture in post hepatitis cirrhosis the fibrous bands contracting and becoming more acellular with the passage of time (Sherlock 1948) It is rare for the inflammatory activity to persist for more than a year after the initial attack

The lesion obeys all the criteria usually accepted for cirrhosis namely proliferation of connective tissue degeneration and death of hepatic cells and regeneration of the liver There is discussion however among pathologists about the identity of this post hepatitis cirrhosis with the classical Laennec variety It is believed that the lesion following acute hepatitis corresponds to the toxic or post necrotic cirrhosis or healed acute yellow atrophy described by Mallory (1911) and Wilson and Goodpasture (1927) The more important diagnostic points are said to be the variable size of the nodules of parenchyma which are not uniformly or diffusely distributed and the different breadth of the connective tissue bands Fatty change if present excludes post hepatitis cirrhosis The difficulties encountered in the pathological diagnosis of the individual case are well shown by the recent investigation conducted by the Macy Foundation (1947) Eight pathologists were presented with 106 hepatic sections and asked to determine the aetiology of the hepatic cirrhosis present Complete agreement on the interpretation of the sections and in particular between a nutritional and an infective cause was achieved in only 19 cases and this was increased to 35 when the gross description of the liver and clinical history of the patient were available It is apparent that in many instances therefore post hepatitis cirrhosis cannot be distinguished from the usual Laennec type

Laennec s cirrhosis may be complicated by primary liver cell carcinoma and this association has also been noted in two cases of post hepatitis cirrhosis (Sheldon and James 1948)

EXTRAHEPATIC LESIONS

The following description is based on the account by Lucke (1944) of the autopsy findings in 125 fatal cases of infective hepatitis

The gall bladder and main bile-ducts show no significant change The regional lymph glands are oedematous and often hyperplasic The spleen enlarges in

FIG 250—Subacute hepatic necrosis A nodule of surviving liver cells is surrounded by a wide area of necrosis The lobular pattern is destroyed H E × 86

FIG 251—Post hepatitis cirrhosis Inflammation is not seen The lobular patt rn is destroyed H E × 43 5

The patient remains clinically jaundiced for 2–4 weeks and the average period of hospitalization is 5 weeks

The differences in the clinical picture of acute infective hepatitis and serum hepatitis are variable and inconstant and do not enable a differential diagnosis to be made Patients with serum hepatitis tend to have a more severe form of the illness This may be due to the underlying poor nutritional status of those con tracting serum jaundice for they are usually having treatment or investigation for some other disease

Hepatitis sine icterus

The above description refers to patients requiring hospitalization These are inevitably the more severely ill It should be realized that a great many patients with acute hepatitis not only have no symptoms of the disease but also overt jaundice This is particularly true of children in whom acute hepatitis is often very mild The only physical findings in these non jaundiced cases is an enlarged tender liver and this also is not constant The faeces show no change in colour Hepatic biopsies have shown that the lesion may be as severe as that encountered in many of the icteric cases (Mallory 1947 Axenfeld and Brass 1942) Cirrhosis is therefore a possible development even after a clinically mild illness These patients moreover are infective as regards serum and excreta and the epi demiological implications are obvious

BIOCHEMICAL CHANGES

Urine

The first abnormality to be detected is the presence of bile pigment in the urine This occurs even before excess urobilinogen is excreted Pollock (1945) found that of 53 patients in the pre icteric phase of acute hepatitis 86 5 per cent had a positive test for bilirubin in the urine while in only 24 per cent was the urine positive for urobilinogen Moreover bilirubin appears in the urine before the total serum bilirubin concentration is raised (Gellis and Stokes 1945) The bilirubinuria is initially so slight that it can only be detected if sensitive tests are applied Suitable methods are the methylene blue test (Gellis and Stokes 1945) Hunter s diazo test (Pollock 1945) or the Harrison spot test (Hawkinson Watson and Turner 1945) Later in the illness bilirubin disappears from the urine even though it remains increased in the blood This suggests that in hepatitis there is a varying urinary threshold for bilirubin In the early stages the threshold is very low so that any bilirubin increase in the blood results in its excretion in the urine and this for a time actually prevents the blood concentration rising Later in the illness with convalescence the urinary threshold increases and bilirubin cannot be found in the urine

In the late pre icteric phase urobilinogen is found in excess in the urine This abnormality follows very closely on the excretion of bile pigment It is due to the damaged hepatic parenchyma being unable to re-excrete in the bile all the uro bilinogen absorbed from the intestines In the majority of patients at the height of the jaundice very little bilirubin is excreted by the liver and urobilinogen dis appears from the urine In these patients the first sign of recovery is the

early cases this is related to cellular *proliferation and in later stages to congestion* The bone marrow is moderately hypoplasic but maturation both of the erythrocytes and granulocytes appears normal In about 15 per cent *of patients* there is a phlegmonous inflammation of the gastro intestinal tract—particularly in the caecal region Casts are found in the distal convulated and collecting tubules of the kidney these are non specific and occur in association with most forms of jaundice Fat storage may also be seen in the proximal tubules The *brain shows an acute* non specific degeneration of ganglion cells and in 15 per cent a mild meningo encephalitis was noted In most instances however the cerebral lesion is neither *sufficiently severe nor specific to warrant the term* meningo encephalitis (Stokes Owen and Holmes 1945)

In fatal cases haemorrhages are found particularly in lungs *intestines epi* cardium endocardium and kidney Ascites is noted in almost two thirds of fatal cases but is a late development

CLINICAL FEATURES

An acute febrile non icteric stage of about one week s duration precedes the *development of jaundice During this phase anorexia nausea and vomiting and* mental depression are conspicuous Rashes appear in about 5 5 per cent of patients and may be urticarial maculopapular or erythematous they are said to be more frequent in serum hepatitis than in the acute infective variety Arthralgias are sometimes noted Occasionally headache with meningismus may be so severe as to cause confusion with true meningitis Later in the prodromal period there may be right upper quadrant abdominal discomfort The urine darkens and the stools become pale It is rare for faecal colour to be as clay coloured as that seen in extrahepatic obstructions of the biliary passages The *temperature returns to normal as the jaundice develops Within a few days the* symptoms abate the appetite returns and abdominal discomfort and vomiting are no longer noted It must be emphasized that the severity and duration of the prodromae are very variable and a great many patients pass through this period entirely symptom free Pruritus may be experienced at the onset of the jaundice but is rare If it persists for more than three days the diagnosis of acute hepatitis should be revised and that of surgical obstructive jaundice considered

The patient should be carefully questioned concerning contact with other cases of jaundice or with children having had recent unexplained gastro intestinal dis *turbance Therapy during* the past 6 months of any type involving puncture of the skin must be noted

Physical signs in the jaundiced stage include a palpable liver in 70 per cent of patients The edge is smooth and tender Even in patients where the liver edge cannot be felt a punch test on the right lower ribs posteriorly causes discomfort The spleen is palpated *in 10–15 per cent of patients The vascular* angiomas (spiders) so characteristic of chronic liver disease are rarely seen in acute hepatitis *although* they may be noted in the severe protracted case They disappear as the patient recovers Lymph glands in the right posterior triangle of the neck can enlarge These glands have contact with the deep lymph channels draining the dome of the liver In adults the weight loss over the period of illness is *about 10 lb*

Whidborne (1946) and Klatskin and Drill (1950) does not support the view that the one minute bilirubin fraction is a chemically distinct entity There seems little practical purpose served in estimating the fractions of "direct" and "indirect" bilirubin in the serum or of performing the van den Bergh reaction in patients with acute hepatitis

Estimation of the total serum bilirubin concentration by a standard diazotization procedure does give some useful information The clinical impression of icterus is confirmed and in general the deeper the jaundice the greater the extent of liver cell destruction (Fig 252) and the more prolonged the clinical course (Sherlock

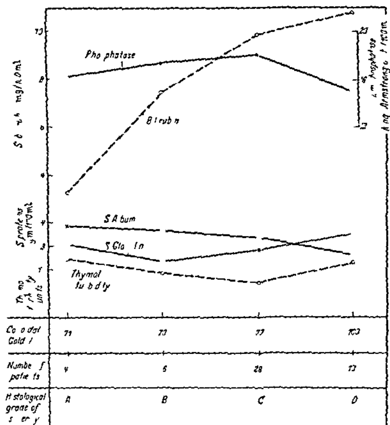


Fig 252 —Composite curve of the mean biochemical results with increasing liver cell damage in 135 patients with acute hepatitis The patients have been graded from A to D with respect to biopsy sections

1946) There are certain exceptions Occasionally in the overwhelming fulminant case death occurs before the patient has time to become jaundiced Sometimes where the disease is more prolonged jaundice may be slight Lawrence (1946) reports the history of a young man in whom relapsing hepatitis with liver cell

reappearance of urinary urobilinogen This can be detected before there is clinical lessening of icterus and is an excellent indication of commencing recovery Once urobilinogen has reappeared, it persists for a time in excess Final complete disappearance of urobilinogen indicates functional recovery of the liver cells and is a good sign of hepatic functional recovery

Although good quantitative methods for the estimation of urobilinogen are available (Watson 1936, Maclagan 1946), these are time-consuming and qualitative techniques are adequate for general clinical purposes Afternoon specimens should be used as in the digestive phase more bile is present in the intestines and hence more urobilinogen is likely to be found in the urine Urobilinogen may be tested qualitatively by Erhlich s aldehyde reagent The urine must be freshly voided and the reagent also should be recently prepared Urobilin an oxidation product of urobilinogen can be tested for by Schlesinger s alcoholic zinc acetate method The urine need not be too fresh and the reagent used is stable This, therefore is the more satisfactory routine test The techniques employed are described in standard textbooks of clinical biochemistry

Other urinary abnormalities found in the more deeply jaundiced patients are albuminuria and the presence of bile stained leucocytes and granular and epithelial casts in the centrifuged urinary deposit These findings are due to a mild renal tubular lesion the so called biliary nephrosis They are not specific to hepatitis but occur in association with all forms of deep jaundice

Faeces

Every stool passed should be inspected and the colour recorded The onset of the jaundiced stage is marked by lightening of the stool colour At the height of the jaundice the stools are often very pale but rarely as pale as those seen in obstructive lesions of the extrahepatic bile passages This phase usually lasts 3–4 days reappearances of pigment in the stools denotes impending recovery and is an excellent prognostic guide Quantitative estimation of stercobilinogen in the stools (Watson 1936 Maclagan 1946) is time-consuming and adds little practical information to that obtained by inspection

Blood

Serum bilirubin.—It is usually accepted that there are two types of bilirubin in the serum which can be distinguished by their respective rates of diazotization in the direct van den Bergh reaction The prompt direct or one minute fraction represents bilirubin that has regurgitated from the biliary tree and the indirect fraction represents retained bilirubin (Ducci and Watson 1945) The bilirubin found in normal serum is of the indirect variety and one of the earliest changes in acute hepatitis is an increase of the one minute fraction (Neefe and Reinhold 1946) However as this is detected after the pigment changes in the urine it is of little practical value in early diagnosis Later the jaundice of hepatitis is very complex bilirubin being retained because of liver cell inadequacy and regurgitated because of bile canalicular rupture and disorganization It proves impossible to evaluate the extent of hepatocellular and cholangiolitic liver involvement by the estimation of the one minute bilirubin fraction Moreover recent work by Gray and

The thymol turbidity test depends mainly on an increase in the proportion of serum (lipoid containing) β globulin (Maclagan 1944 Kunkel and Hoagland 1947) It is particularly positive in acute inflammatory liver disease rather than in the chronic degenerative disorders such as alcoholic cirrhosis (Cohen and Thomp on 1947) It tends to become positive later in the course of the disease than the tests depending on γ globulin changes but remains positive for a longer time A positive thymol turbidity test is not a contra indication to commencing convalescence

In acute hepatitis it is useful to perform two serocoagulation tests one such as the zinc sulphate or cephalin cholesterol test for early diagnosis and the thymol turbidity test not only for diagnosis but also as an indication of continuing inflammatory activity

The bromsulphalein test —This test is used to determine whether the liver can excrete bile pigment It is therefore of little use in the jaundiced phase It may be used in the pre icteric stage as a diagnostic aid and later when the jaundice has almost disappeared as a guide to convalescence The material is expensive and difficult to get in Great Britain and this test although of value in the diagnosis of well compensated hepatic cirrhosis has little practical value in the study of acute hepatitis

Biochemical tests conclusion

These tests are performed for two purposes to assist diagnosis and to determine the severity of the attack and hence enable a prognosis to be formulated The biochemical methods used should be the minimum commensurate with these aims A suggested practical routine is shown in Table II More complicated procedures such as the estimation of cholesterol esters the galactose and laevulose tolerance tests and the hippuric acid synthesis test give little additional information and the place of the laboratory in the clinical study of acute hepatitis has been over emphasized The illness in the majority of patients can be diagnosed and

TABLE II

A Suitable Routine for the Investigation of a Patient with Infective Hepatitis

Test		*Value*	*Interval*
S total bilirubin	–	Confirm jaundice Assess severity	weekly
S alk phosphatase	–	Diagnosis	weekly
S albumin –	–	Assess severity	weekly
Thymol turbidity test	–	Diagnosis	weekly
Colloidal gold test	–	Diagnosis	weekly
Stool colour	–	Diagnosis	daily
Urinary bilirubin	–	Early diagnosis	early
Urinary urobilin (qualitative)	–	Early diagnosis	daily
Bromsulphalein test	–	Prognosis	convalescence

failure persisted for 6 months but at no time was there clinical icterus The diagnosis of subacute necrosis was confirmed at autopsy Lawrence discovered 12 similar instances in the literature The explanation is unknown

The height of the serum bilirubin concentration gives some indication of progress Convalescence cannot be undertaken till the level is less than 2 milligrams per hundred millilitres and preferably the value should be less than 1 milligram per hundred millilitres

Serum alkaline phosphatase shows a slight increase but the values realized are usually less than those found in surgical obstructive jaundice If an arbitrary dividing line of 30 King Armstrong units per 100 millilitres is taken then the majority of patients with acute hepatitis have values less than this and most patients with obstructive jaundice give values greater than 30 units per 100 millilitres (Fig 252) (Sherlock 1946) Maclagan (1947) finds 25 King Armstrong units per 100 millilitres serum alkaline phosphatase a satisfactory dividing line

There are two possible explanations for the increased serum phosphatase in acute hepatitis If the phosphatase is formed mainly outside the liver and is excreted by the bile then the rise in the serum in hepatitis is due to the injured liver cells being inadequate to excrete all that formed Biliary obstruction due to distortion of canaliculi may also play a part If the liver cells or bile passages produce the phosphatase then the intrahepatic biliary obstruction of hepatitis is an important factor in the production of the increased values Histochemical studies show that the phosphatase in the liver increases in hepatitis It is found in sinusoids and liver cells but not in the bile channels (Sherlock and Walshe 1947) This supports the first hypothesis that in hepatitis the injured liver cells are unable to excrete the alkaline phosphatase formed elsewhere

Serum alkaline phosphatase falls slowly after recovery from hepatitis The liver finds it more difficult to excrete phosphatase than bilirubin A raised serum phosphatase is a contra indication to the initiation of convalescence

Serum protein—The estimation of either total or differential serum proteins is of little practical diagnostic value as many patients with hepatitis have values well within the normal range There is however a good correlation between the severity and the serum albumin concentration This protein fraction is probably manufactured solely in the liver and in severe hepatic necrosis it is significantly depressed (Fig 252) This is particularly true of patients with a prolonged course when the serum albumin level gives considerable prognostic information Liver cell failure must persist some time before a lowered serum albumin occurs and patients with a fulminating hepatitis often show normal values

Serocoagulation tests—Although the serum proteins may be quantitatively within the normal range electrophoretic analysis shows abnormalities Apart from the inconstant lowered serum albumin there are increases in the β globulin and γ globulin components (Martin 1946) These account for the positivity of various flocculation tests The cephalin cholesterol tests (Hanger 1939 Moore Pierson Hanger and Moore 1945) the colloidal gold test (Maclagan 1944) and the zinc sulphate test (Kunkel Andrews and Eisenmenger 1948) depend on an increase in the γ globulin component and to a lesser extent on diminution and alteration in the character of the serum albumin These tests tend to be positive early in the disease and are of considerable diagnostic value

bile salts in the blood might be the mechanism involved in the low F S R of acute hepatitis However the amounts of bile salts added (20 milligrams per hundred millilitres) were far above those encountered in acute hepatitis (Sherlock and Walshe 1947) and this explanation does not seem valid The altered physico chemical composition of the plasma proteins in acute hepatitis seems a more reasonable mechanism for the E S R changes

Interstitial fluid and sex hormone changes—During the icteric phase of acute hepatitis there is an increase in the interstitial fluid compartment of the body and a tendency to store water as measured by a standard water tolerance test During recovery there is a diuresis These changes are independent of protein abnormalities and may have an endocrine cause It seems possible that the liver in hepatitis is not able to inactivate either oestrogens or the anti diuretic hormone of the posterior pituitary (Labby and Hoagland 1946) Support for this former hypothesis is found in the urinary output of sex hormones in hepatitis Young adult males show a fall in their urinary 17 ketosteroid output with a rise in urinary oestrogens (Gilder and Hoagland 1946) These changes occur at the height of the illness and are proportional to the clinical severity

Oral cholecystography—The serum total bilirubin concentration must be less than 11 milligrams per hundred millilitres and the bromsulphalein retention test less than 30 per cent of the injected dose if the gall bladder is to be visualized This can be most satisfactorily shown in 90 per cent of patients after an oral dose of radio opaque iodine containing dye (Readinger and others 1950) This is still further evidence against the bile duct catarrh hypothesis of infective hepatitis

CLINICAL ASPECTS OF THE COMPLICATIONS OF ACUTE HEPATITIS

Relapses—Occasionally just as the patient seems to be making a good recovery from the acute attack there is a recrudescence All the original prodromal symptoms are experienced the temperature rises and this is followed by a deepening of jaundice The relapse is often precipitated by premature activity or by the intake of alcohol It is usually milder and runs a shorter course than the original acute episode Further relapses can occur in the same patient Aspiration liver biopsy sections show similar histological changes to those described in the original attack (Mallory 1947) It seems probable that the prolonged relapsing type of acute hepatitis is more likely to be followed by an hepatic cirrhosis than is the initially severe episode which makes a quick uneventful recovery

Acute hepatic necrosis (fulminant hepatitis)—This applies to acute hepatitis fatal within 3 weeks of the onset The clinical course has been well described by Lucke and Mallory (1946) and Snavely (1950) There are all grades of severity In the most fulminant type the patient relapses into coma within 2–3 days of the onset of the illness and is dead almost before jaundice can develop Maniacal excitement may precede the coma and in this state the patient may be wrongly diagnosed as a psychiatric illness More usually the disease seems to be running its usual course when some untoward features are noted These are often persistent vomiting or neurological changes These latter include drowsiness and mental depression alternating with periods of delirium and excitement tremors and rigidity with pyramidal tract signs (Turner and others 1944 Stokes and others

followed by careful history and examination *together with routine* examination of the urine and faeces

There are no biochemical differences between homologous serum hepatitis and acute infective hepatitis

ASPIRATION LIVER BIOPSY IN THE DIAGNOSIS OF HEPATITIS

This procedure always enables acute hepatitis to be distinguished from other forms of jaundice (Sherlock 1945) In the average case however this diagnosis can be readily made by clinical and biochemical means Haemorrhage from the inflamed liver of acute hepatitis is a more frequent sequel of aspiration biopsy than it is in other conditions Aspiration liver biopsy should therefore, be confined to those cases of jaundice *in which diagnosis even after adequate clinical* study remains obscure The particular value of aspiration biopsy is in the diagnosis of post hepatitis cirrhosis from the less serious sequelae of acute hepatitis

SEROLOGICAL TESTS

Attempts to find a complement fixation test useful in the diagnosis of acute hepatitis have failed (Oliphant Gilliam and Larson 1943 Miles 1946)

Very recent work suggests that the agent of infective hepatitis can be grown on tissue culture and this followed by passage in the amniotic cavity of the chick embryo This material given to volunteers produces an illness closely resembling natural hepatitis but without jaundice (Henle and others 1950b Drake and others 1950) A *skin test antigen prepared from the amniotic fluid of infected chicks* gives positive skin reactions in all individuals with a past history of spontaneous or induced hepatitis In contrast the incidence among cases of post serum hepatitis was no greater than among adults chosen at random (Henle and others 1950b) These observations are still in the preliminary stage but if confirmed are obviously of great practical importance in *the diagnosis of hepatitis*

HAEMATOLOGICAL CHANGES

In the pre icteric stage there is a leucopenia lymphopenia and neutropenia and this reverts towards *normal* as the jaundice appears *In 5–20 per cent of patients* atypical lymphocytes resembling those of infectious mononucleosis appear in the *peripheral blood*

The prothrombin time is diminished in the more severe cases and does not return to normal with vitamin K therapy Anaemia appears only in protracted severe illness and can usually be related to blood loss

The sedimentation rate of the red cells (E S R) is high in the pre icteric phase and falls as the jaundice develops This depression of the E S R in the first few days is often useful in the diagnosis of acute hepatitis from malaria and other pyrexias (Wood 1945) As the jaundice abates the E S R rises to fall again to normal with complete recovery A sustained *high E S R* is a *useful indication of* continuing hepatic inflammation Miles (1945) showed that the E S R could be depressed by the addition of crude bile salts to blood He suggested that increased

features are those of subacute necrosis right upper quadrant pain being the only unusual feature Death occurs after a course of 4–9 months often in hepatic failure The mortality rate is about 50 per cent and the liver at autopsy shows the features of subacute hepatic necrosis It seems likely that the condition is a variant of acute infective hepatitis

Post hepatitis cirrhosis—Long term sequelae with an organic basis occasionally develop after acute virus hepatitis The pathological sequence from the acute lesion through subacute necrosis to cirrhosis has already been described and the clinical features are detailed in Section II of this chapter Cirrhosis usually follows a severe protracted and relapsing attack of acute hepatitis A mild initial lesion however should not exclude consideration of a subsequent cirrhosis which has been reported after a remarkably mild clinical course (Sherlock 1948) The cirrhosis may present in various ways The acute hepatitis may pass into a sub acute stage which as it continues becomes indistinguishable from cirrhosis These patients show all the features of liver cellular inadequacy This is the rarer course and more usually the patient makes an apparently good clinical recovery from a severe attack of hepatitis only to appear months or years later with the features of portal venous hypertension During the intervening period there are no clinical symptoms and physical findings are confined to hepatomegaly and splenomegaly and are not constant The intrahepatic obstruction to the portal vascular tree produced by the scarring of the cirrhosis leads to gastro intestinal bleeding and this is the usual mode of presentation The development of cirrhosis with mainly hepatocellular failure some time after acute hepatitis has been reported (Sheldon and James 1948) but is rather unusual

It must be emphasized that cirrhosis is a rare complication of acute hepatitis The exact incidence is unknown The majority of patients having persistent symptoms after an attack of hepatitis when investigated fully are found to have normal liver function and structure

Watson and Hoffbauer (1946) describe a group of patients in whom antecedent jaundice probably infective hepatitis is followed by chronic icterus with pruritus and hepatosplenomegaly There is no ascites Biochemical studies show high serum alkaline phosphatase total cholesterol bile acid and globulin concentration The lesion is said to be in the cholangioles with sparing of the hepatic parenchyma It has been termed cholangiolitic biliary cirrhosis The existence of such a clinical syndrome is not in doubt and is probably synonymous with Hanot s cirrhosis or xanthomatous biliary cirrhosis (MacMahon and Thannhauser 1949) If this is a complication of virus hepatitis however it is surprising that the condition has not been seen more recently among the large number of sufferers in the war time epidemics of virus hepatitis The syndrome can certainly occur in patients who have never suffered from acute hepatitis Up to the present time the causative relationship of acute hepatitis to this cholangiolitic lesion has not been proved

Post hepatitis syndrome

Occasionally a disability develops after acute hepatitis in patients in whom there is no hepatic cirrhosis and in fact no organic liver lesion The condition has been designated the post hepatitis syndrome (Caravati 1944 Sherlock and Walshe

1945) The jaundice deepens and clinically the liver appears to regress under the right costal margin Haemorrhages occur in almost any site The most common are in the skin causing purpura or bruising in the brain causing focal cerebral signs and in the gastro intestinal tract causing haematemesis and melaena The bleeding can be related to the very low prothrombin time which develops in these severe cases although alterations in accessory coagulation factors may also play a part The blood shows a leucocytosis which contrasts with the usual leucopenia of hepatitis The urine output falls and there may be frank anuria *Ascites* is a late development and is more frequently found in the more prolonged subacute types of illness Finally coma deepens and the patient is usually dead within about 10 days there being *a terminal rise in temperature The clinical features are simply* those of liver failure and cannot be distinguished from such failure due to other causes for instance hepatic cirrhosis or Weil s disease

The biochemical changes are interesting but do not offer an explanation for the hepatic coma The liver cannot deaminate amino acids to form urea and these substances accumulate in the blood and are passed in the urine The blood amino acid nitrogen rises and the actual amino acids in blood and urine can be identified by paper chromatography (Dent 1949) Leucine and tyrosine crystals are classically described in the urine in hepatic coma but are in practice excessively rare Blood urea surprisingly does not fall perhaps because of the kidney failure occurring simultaneously with that of the liver The blood glucose concentration is often normal but this finding is difficult to evaluate as most patients in hepatic coma are receiving glucose therapy

Subacute hepatic necrosis

Acute hepatitis can show all gradations of severity between the fulminating disease described above and subacute hepatic necrosis in which a relapsing illness *continues for about 3 months before the fatal outcome* The illness starts in a similar fashion to the ordinary attack of acute hepatitis However instead of recovery jaundice fluctuates and the patient continues ill The jaundice in spite of variations is persistent and deep Vascular angiomas (spiders) develop The liver is enlarged and the edge is tender sometimes nodules of hyperplasia are palpable Splenomegaly is constant Ascites develops and with it oedema of the legs The urine shows both urobilin and bilirubin *The sedimentation rate of the* erythrocytes is raised and there may be slight fever Biochemical tests reflect the gross disturbance in liver cell function the plasma proteins being particularly affected with low serum albumin concentrations a high serum globulin and positive serocoagulation tests Death usually occurs in liver failure Hypo prothrombinaemia is constant and some patients die from haemorrhage usually from the gastro intestinal tract Other patients die of intercurrent infections The disease however is not invariably fatal and quite remarkable recoveries are sometimes noted Complete restitution of the liver to normal is impossible after subacute necrosis and a subsequent hepatic cirrhosis is inevitable The activity of this lesion is however variable

Recently epidemics of a particular type of subacute hepatic necrosis have been reported from Scandinavia (Alsted 1947 Bjorneboe and others 1948) This malignant hepatitis affects mainly women past the menopause The clinical

features are those of subacute necrosis right upper quadrant pain being the only unusual feature Death occurs after a course of 4-9 months often in hepatic failure The mortality rate is about 50 per cent and the liver at autopsy shows the features of subacute hepatic necrosis It seems likely that the condition is a variant of acute infective hepatitis

Post hepatitis cirrhosis —Long term sequelae with an organic basis occasionally develop after acute virus hepatitis The pathological sequence from the acute lesion through subacute necrosis to cirrhosis has already been described and the clinical features are detailed in Section II of this chapter Cirrhosis usually follows a severe protracted and relapsing attack of acute hepatitis A mild initial lesion however should not exclude consideration of a subsequent cirrhosis which has been reported after a remarkably mild clinical course (Sherlock 1948) The cirrhosis may present in various ways The acute hepatitis may pass into a sub acute stage which as it continues become indistinguishable from cirrhosis These patients show all the features of liver cellular inadequacy This is the rarer course and more usually the patient makes an apparently good clinical recovery from a evere attack of hepatitis only to appear months or years later with the features of portal venous hypertension During the intervening period there are no clinical symptoms and physical findings are confined to hepatomegaly and splenomegaly and are not constant The intrahepatic obstruction to the portal vascular tree produced by the scarring of the cirrhosis leads to gastro intestinal bleeding and this is the usual mode of presentation The development of cirrhosis with mainly hepatocellular failure some time after acute hepatitis has been reported (Sheldon and James 1948) but is rather unusual

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Post hepatitis syndrome

Occasionally a disability develops after acute hepatitis in patients in whom there is no hepatic cirrho i and in fact no organic liver lesion The condition has been designated the post hepatitis syndrome (Caravati 1944 Sherlock and Walshe

1946) The most prominent features are anxiety and apprehension of future jaundice fatigue failure to regain the weight lost during the acute stage anorexia with fat intolerance and right upper abdominal discomfort The only positive physical finding is a palpable sometimes tender liver edge This is more often due to powerful diaphragmatic movements with downward displacement of a normal sized liver than to actual hepatomegaly Biochemical tests on urine and serum are usually within the normal range

Hepatic sections obtained by biopsy show histology that does not differ from that found in patients who have recovered from acute hepatitis and are now

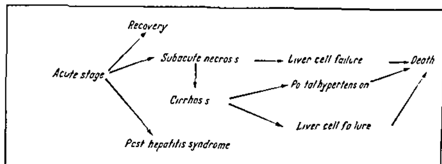


FIG 253 —The clinical course of acute infective hepatitis

symptom free The symptoms can usually be related to psychogenic causes and this condition is much more common in the Forces than in civilian practice Symptoms rarely persist for longer than one year after the original attack of hepatitis Treatment consists of reassurance after the fullest possible investigation Aspiration liver biopsy is usually necessary to distinguish this condition from a well compensated post hepatitis cirrhosis

The clinical course of acute hepatitis is shown in Fig 253

TREATMENT OF ACUTE HEPATITIS

Prophylaxis of acute hepatitis

Infective hepatitis is spread by faecal contamination usually of food or water Its control lies in perfect sanitation The virus is particularly resistant to ordinary methods of water sterilization and these may not be adequate (Neefe and Stokes 1945) Boiling of water for 5 minutes is a definite safeguard Ultimate control lies in general bodily hygiene and safe disposal of faeces

Homologous serum hepatitis is controlled by avoiding contamination by blood products of any material or object that may be employed parenterally Syringes and needles should be used on only one occasion and re sterilized preferably individually by dry heat Boiling is again an adequate safeguard Stilettes for skin puncture should be discarded after each prick Blood donors must be carefully selected and not allowed to give blood if they are in contact with a patient of jaundice or are feeling off colour or have had jaundice during the previous 6 months As there is little factual evidence of the duration of viraemia after acute hepatitis it is probably wise to exclude all persons known to have ever had the

disease Even this precaution will not entirely prevent spread of the disease by transfusion for healthy carriers who have apparently never had the disease overtly are recorded Havens (1949) estimates that 0 5 per cent of the normal population harbour the virus of hepatitis in their blood without associated symptoms One such long term carrier a professional blood-donor is known to have spread the disease over a period of 3 years (Neefe 1949) Plasma infusions are much more dangerous than blood transfusions and if possible should be avoided Where plasma is used it should be obtained from as small a pool of donors as possible Ultra violet radiation of plasma has been said to probably inactivate the virus of hepatitis (Blanchard and others 1948) This procedure of course cannot be applied to whole blood However there is unequivocal evidence that ultra violet light does not destroy the hepatitis virus in serum or plasma (Barnett Fox and Snavely 1950 James Korns and Wright 1950 Rosenthal Bassen and Michael 1950) Chemical sterilization of blood or blood plasma with chemicals of the nitrogen mustard group may become possible in the future (Hartman and others 1949) At present the only safe blood product for parenteral use is human serum albumin which unfortunately is not commercially available in this country Any candidate for plasma or blood therapy should be carefully considered in the light of the unfortunate hazard of resultant jaundice This form of therapy should not be given empirically as a tonic but only where there is a clear indication

Another therapeutic weapon is available for the control of infective hepatitis epidemics This is the prophylactic administration of immune serum γ globulin The antibodies so introduced may neutralize the hepatitis producing agent This procedure is particularly applicable to schools institutions and camps where an epidemic of jaundice starts and there is a large population at risk If two intramuscular injections of γ globulin are given on successive days to patients within 17 days of exposure to the infective hepatitis virus an immunity is induced from about 6–8 weeks (Gellis and others 1945 Havens and Paul 1945) Large scale studies on squadrons in the Mediterranean theatre and in a children s home have definitely proved the efficacy of this method Unfortunately results for the prevention of homologous serum hepatitis are very poor and the γ globulin did not significantly reduce the incidence of jaundice in a large group of battle casualties The only effect was prolongation of the incubation period (Duncan and others 1947)

Treatment has little effect in altering the course of the ordinary case of acute hepatitis Bed rest is the most valuable therapeutic weapon It should be continued until the patient is symptom free the liver is no longer tender and urobilin has disappeared from the urine The serum bilirubin concentration should be less than 1 milligram per hundred millilitres Bradley (1945) suggests a physiological reason for the value of bed rest He found that in normal subjects the blood flow through the liver was greater in the recumbant than in the erect posture The greater the blood flow through an inflamed organ the more rapidly will healing occur Premature exercise is believed to precipitate relapses but this may depend on the stage at which the exercise is undertaken A study was made of 3 614 patients with acute hepatitis among the United States Occupation Forces in Germany (Swift and others 1950) If the serum bilirubin concentration was greater than 3 milligrams per hundred millilitres then exercise increased the duration of invalidism

by 2 weeks If less than 3 milligrams per hundred millilitres exercise had no effect regardless of the maximum serum bilirubin value previously attained Untoward effects of exercise in the presence of deep jaundice were anorexia hepatic tenderness and an increase in bromsulphalein retention Swift and others therefore advocate a less conservative regime than is usually adopted for previously healthy young adults contracting infective hepatitis

The traditional diet for patients suffering from acute hepatitis has been one low in fat and high in carbohydrate content There is no positive evidence that this regime is of therapeutic value No benefit can be attributed to lowering the fat intake A comparison was made of the effects of a diet low in fat (50 grams daily) and high in fat (150 grams daily) on patients suffering from infective hepatitis The protein intake was high and constant for the two diets (150 grams daily) The high fat diet actually proved advantageous the patients receiving it gaining more weight and attaining a normal bromsulphalein test sooner (Hoagland and others 1946) These favourable results may be attributed to a higher caloric intake on the high fat diet No benefit can be attributed to a high protein diet Darmady (1945) studied test and control groups among Royal Air Force men with hepatitis and showed that the course of the illness was not altered by giving a high protein diet with supplements of the vitamin B complex and liver extract A rational diet in hepatitis should contain 300 grams carbohydrate and 90–120 grams protein It can be composed of whatever foods the patient wishes In the early stages anorexia is absolute and the patient must be tempted to eat Later the appetite is voracious and should be satisfied A high caloric intake will facilitate the gain of weight lost and will speed up recovery Convalescence should continue for at least twice as long as the period of bed rest Alcohol is well known to cause relapses and should be abstained from for at least 6 months after the acute attack

Supplementary amino acids and lipotropic agents have been extensively tried in the treatment of hepatitis The patients have shown little benefit from the therapy The failure of methionine to influence the course of the disease has been reported by Wilson Pollock and Harris (1945) and Higgins O Brien Stewart and Witts (1944) Cysteine seemed to be beneficial in the group studied by Wilson Pollock and Harris (1946) but this was mainly due to the greater number of relapses among the controls If relapses are excluded the differences almost disappear Peters and others (1945) showed a slight but significant increase in the rate of recovery of patients suffering from arsenotherapy jaundice given cysteine or methionine casein had no effect The substances were given to provide sulphydryl groups for the removal of arsenic It was later realized that the disease was infective and this explanation was no longer cogent Choline has proved of little value (Richardson and Suffern 1945 Hoagland and Shank 1946) It is perhaps not surprising that these lines of therapy have proved so valueless The general population of Great Britain is not suffering from protein malnutrition and the amino acid reserves are adequate supplements to speed up recovery from hepatitis are not required The liver in acute hepatitis does not show fatty change and extra lipotropic agents such as choline are unnecessary

Antibiotics have been tried in the treatment of acute hepatitis but their position is at present uncertain Of those at present available aureomycin may be of most

value It had no real effect on the patients treated by Shaffer and others (1950) but results from a larger number of patients are needed before it can be discarded One case of post hepatitis cirrhosis showed benefit with aureomycin (Rumball and others 1950)

TREATMENT OF HEPATIC COMA (ACUTE LIVER FAILURE)

Hepatic coma carries such a high mortality rate that in spite of the lack of specific treatment the physician is usually forced to adopt more active lines than those employed in the ordinary case of acute hepatitis Great care must be taken to avoid over treatment and the conservative measures that have proved so successful in the treatment of renal failure should be applied to the treatment of hepatic failure The liver is thus forced to do the minimum of metabolic work

Glucose is given in amounts sufficient to provide an energy source comparable to that provided by the healthy liver in a 70 kilograms man this is estimated at about 350 grams daily (Bondy James and Farrar 1949) It is given continuously intravenously or by intragastric tube in 10 per cent solution about 3 litres daily are required One litre contains also 0 9 per cent sodium chloride each litre has added to it one gram of potassium chloride to prevent depletion as the utilization of glucose involves the uptake of potassium from the extracellular fluids Great care must be taken that the circulation is not overloaded with fluid and that oedema of the lungs does not occur Blood transfusion is indicated only if there is haemorrhage or anaemia Vitamin K is given daily in 10 milligram doses intramuscularly in the presence of the damaged liver it will not necessarily restore the prothrombin time to normal Penicillin is given routinely to combat broncho pneumonia

The periods of manic excitement demand sedation and the selection of a suitable drug is often difficult The liver detoxicates morphine and barbiturates and these substances are tolerated poorly by the patient with hepatic failure Paraldehyde is the safest drug to use Many patients have been killed by injudicious sedation and it is better to have a restless patient than one overdosed with sedatives

The blood amino acids are high in hepatic coma and cannot be utilized by the failing liver Administration of further amino acids is merely an extra strain on the liver

Other therapeutic measures that must be considered are aureomycin and adrenocorticotrophic hormone (ACTH) Gyorgy and others (1950) showed that aureomycin would prevent the hepatic necrosis in rats produced by a necrogenic diet In man aureomycin has been used in four instances of hepatic coma in three of which there was a good effect (Farquhar and others 1950) Obviously experience will have to be extended before the place of aureomycin can be fully assessed The use of ACTH is on even less secure ground but in such a fatal condition as hepatic failure any therapeutic weapon which will bolster up regeneration and reaction to injury must be considered

REFERENCES

Alsted G (1947) *Amer J Med Sci* **213** 257
Anon (1948) *J Amer Med Ass* **137** 1077
Axenfeld H and Brass K (1947) *Frankfurt Ztschr f Path* **57** 147
— — (1944) *Ibid* **58** 220

Aycock W L and Oren F W (1947) *Amer J Med Sci* **214** 483
Barnett R N Fox R A and Snavely J G (1950) *J Amer Med Ass* **144** 226
Beeson P B Chesney G and McFarlan A M (1943) *Lancet* **1** 814
Bjorneboe M Jersild M Lundbaek K Thaysen E H and Ryssing E (1948) *Ibid* **1** 867
Blanchard M C Stokes J Jun Hampil B Wade P R and Spizizen J (1948) *J Amer Med Ass* **138** 341
Bondy P K James D F and Farrar B W (1949) *Ibid* **28** 238
Bradley S E Ingelfinger F J Bradley G P and Curry J J (1945) *Ibid* **28** 890
— (1948) *Trans 7th Conf Liver Injury* p 53 Josiah Macy Jun Foundation New York
Caravati C M (1944) *Southern Med J* **37** 251
Cohen P C and Thompson F (1947) *J Lab clin Med* **32** 314
Darmady E M (1945) *Brit Med J* **1** 795
Dent C E (1949) *Biochem Soc Symp No* **3** Cambridge University Press
Dible J H McMichael J and Sherlock S P V (1943) *Lancet* **2** 402
Drake M E Kitts A W Blanchard M C Farquhar J D Stokes H Jun and Henle W (1950) *J exp Med* **92** 283
Ducci H and Watson C J (1945) *J Lab clin Med* **30** 293
Duncan G G Christian H A Stokes J Jun Rexer W F Nicholson J T and Edgar A (1947) *Amer J Med Sci* **213** 53
Eppinger H (1937) *Die Leberkrankheiten J* Vienna Springer
Farquhar J D Stokes J Jun Whitlock C M Jun Bluemle L W Jun and Gambescia J M (1950) *Amer J Med Sci* **220** 166
Ford J C (1943) *Brit Med J* **1** 675
Gardner H T (1950) *Amer J Med* **8** 516
Gellis S S and Stokes J Jun (1945) *J Amer Med Ass* **128** 782
— — Brother G M Hall W M Gilmore H G Beyer E and Morrissey R A (1945) *Ibid* **128** 1062
Gilder H and Hoagland C L (1946) *Proc Soc exp Biol N Y* **61** 62
Gray C H and Whidborne J (1946) *Biochem J* **40** 81
Gyorgy P Stokes J Jun Smith W H and Goldblatt H (1950) *Amer J Med Sci* **220** 6
Hanger F M (1939) *J clin Invest* **28** 261
Hartman F W Mangum G H Feeley N and Jackson E (1949) *Proc Soc exp Biol N Y* **70** 248
Havens W P Jun and Paul J R (1945) *J Amer Med Ass* **129** 270
— (1947) *Ibid* **134** 653
— (1948) *Medicine* **27** 279
— (1949) *Pennsylvania Med J* **52** 1653
Hawkinson V Watson C J and Turner R H (1945) *J Amer Med Ass* **129** 514
Henle W Harris S Henle G Harris T N Drakes M E Mangold F and Stokes J Jun (1950a) *J exp Med* **92** 271
Henle G Drake M Henle W and Stokes J Jun (1950b) *Proc Soc exp Biol N Y* **73** 603
Higgins G O Brien J R P Stewart A and Witts L J (1944) *Brit Med J* **1** 211
Himsworth H P and Glynn L E (1944) *Clin Sci* **5** 93
Hoagland C L Labby D H Kunkel H G and Shank R E (1946) *Amer J Publ Hlth*
— and Shank R E (1946) *J Amer Med Ass* **130** 615
James G Korns R F and Wright A W (1950) *Ibid* **144** 228
Klatskin G and Drill V A (1950) *J clin Invest* **29** 660
Kunkel H G and Hoagland C L (1947) *Ibid* **26** 1060
— Andrews E H Jun and Eisenmenger W J (1948) *Gastroenterology* **11** 499
Labby D H and Hoagland C L (1946) *Proc Soc exp Biol N Y* **63** 110
Lawrence J S (1946) *Lancet* **1** 41
LeHane D Kwantes C M S Upward M G and Thompson D R (1949) *Brit Med J* **11** 572
Lucké B (1944) *Amer J Path* **20** 471
— and Mallory T (1946) *Ibid* **22** 867
Lurman A (1885) *Berl klin Wschr* **22** 20
MacCallum F O (1944) *Proc R Soc Med* **37** 449
— (1945) *Lancet* **1** 342

Maclagan N F (1944) *Brit J exp Path* **25** 15
— (1944) *Ibid* **25** 234
— (1946) *Ibid* **27** 190
— (1947) *Brit Med J* **2** 197
MacMahon H E and Thannhauser S J (1949) *Ann Med* **30** 121
Macy Foundation Report on Liver Injury *Transactions of the Sixth Conference* 1947 p 9
Mallory F B (1911) *Bull Johns Hopk Hosp* **22** 69
Mallory T B (1947) *J Amer Med Ass* **134** 655
Martin N H (1946) *Brit J exp Path* **27** 363
Miles J A R (1945) *Brit Med J* **1** 707
— (1946) *Brit J exp Path* **27** 25
Moore D B Pierson P S Hanger F M and Moore D H (1945) *J clin Invest* **24** 92
Neefe J R and Stokes J (1945) *J Amer Med Ass* **128** 1063
— and Reinhold J G (1946) *Gastroenterology* **1** 393
— Gellis S S and Stokes J Jun (1946) *Amer J Med* **1** 3
— (1949) *Ann intern Med* **31** 857
Oliphant J W Gilliam A G and Larson C L (1943) *Public Health Reports* **58** 1233
Peters R A Thompson R H S King A J Williams D I and Nicol C S (1945) *Quart J Med* **14** 35
Pollock M R (1945) *Lancet* **2** 626
Propert S A (1938) *Brit Med J* **1** 19
Readinger H M Swift W E Jun Gardner H T and Sheedy J A (1950) *Amer J Med* **8** 611
Richardson J S and Suffern W S (1945) *Brit Med J* **2** 156
Roholm K and Iversen P (1939) *Acta Path Microbiol scand* **16** 427
Rosenthal N Bassen F A and Michael S R (1950) *J Amer Med Ass* **144** 224
Rumball J M Marion D F and Sanders M (1950) *Gastroenterology* **14** 432
Salaman M H King A J Williams D I and Nicol C S (1944) *Lancet* **2** 7
Shaffer J M Farquhar J D Stokes J Jun and Sborov V M (1950) *Amer J Med Sci* **220** 1
Sheldon W H and James D F (1948) *Arch intern Med* **81** 866
Sherlock S (1945) *Lancet* **2** 397
— (1946) *J Path Bact* **58** 523
— (1948) *Lancet* **1** 817
— and Walshe V M (1946) *Ibid* **2** 482
— — (1947) *J Path Bact* **59** 615
— — (1948) *Clin Sci* **6** 223
Snavely J R (1950) *Amer J Med Sci* **219** 89
Stokes J Jun Blanchard M Neefe J R Gellis S S and Wade G R (1948) *J Amer Med Ass* **138** 336
Stokes J F Owen J R and Holmes E G (1945) *Brit Med J* **2** 642
Swift W E Jun Gardner H T Moore D J Streitfeld F H and Havens W P Jun (1950) *Amer J Med* **8** 614
Turner R H Snavely J R Grossman E B Buchanan R N and Foster S O (1944) *Ann intern Med* **20** 193
Van Beek C and Haex A J C (1943) *Acta Med scand* **114** 557
Virchow R (1865) *Virchows Arch* **32** 117
Watson C J (1936) *Amer J Clin Path* **6** 458
— and Hoffbauer F W (1946) *Ann intern Med* **25** 195
Wilson J D and Goodpasture E W (1927) *Arch intern Med* **40** 377
Wilson C Pollock M R and Harris A D (1945) *Brit Med J* **1** 400
— — — (1946) *Lancet* **1** 881
Wood P (1945) *Brit Med J* **1** 2

SECTION II

HEPATIC CIRRHOSIS

SHEILA SHERLOCK

THE stony hard liver with dropsy is said to have been known to Erasistratus of Alexandria nearly three centuries B C Laennec coined the term cirrhosis because the projecting nodules were of fawn or yellowish russet, bordering on the greenish Although fibrosis was later found to be an important part of the lesion the term cirrhosis was too firmly established to be displaced

Hepatic cirrhosis has now become a term applied to chronic diffuse liver disease of varied aetiology There are variations in the different forms of cirrhosis but all have a common background of hepatic histology The essential lobular pattern of the liver is disturbed there is connective tissue proliferation with degeneration death of some liver cells and regeneration of others (Moon 1932) Any pathological lesion in the liver obeying these criteria is entitled to the name cirrhosis

AETIOLOGY AND PATHOLOGY OF CIRRHOSIS

(1) Classic portal or Laennec s cirrhosis (a) post hepatitic (b) dietetic, (c) alcoholic and (d) Banti s syndrome
(2) Cardiac cirrhosis
(3) Haemochromatosis
(4) Biliary cirrhosis
(5) Bilharzial cirrhosis
(6) Hepatolenticular degeneration (Kinnier Wilson s disease)
(7) Other postulated causes of cirrhosis

(1) "Classic portal' or Laennec s cirrhosis

(a) *Post hepatitic cirrhosis*

Acute infective hepatitis is usually followed by complete restoration of the liver to normal However long term sequelae are not unknown and in many instances hepatic cirrhosis can be directly related to a preceding acute infective hepatitis (Jones and Minot 1923 Rennie 1945) In these patients the liver shows destruction of the normal reticulin framework of the lobule with nodular regeneration of surviving liver cells and the development of a true hepatic cirrhosis (Sherlock 1948) (Figs 254–257) The development of cirrhosis after infective hepatitis has been described in detail in another chapter

The exact importance of acute viral hepatitis in the aetiology of cirrhosis remains uncertain Ratnoff and Patek (1942) elicited a past history of jaundice in only 6 5 per cent of 356 patients with cirrhosis Howard and Watson (1947) however obtained a history of previous infective hepatitis in 17 per cent of patients with cirrhosis contrasted with 3 per cent in a similar group without hepatic disease

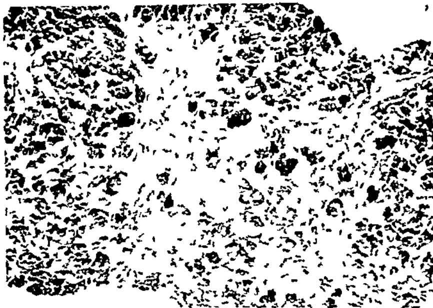


Fig 254—Acute serum hepatitis tenth day of jaundice severe acute hepatitis with groups of liver cells surviving in wide areas of necrosis Best s carmine stain × 115

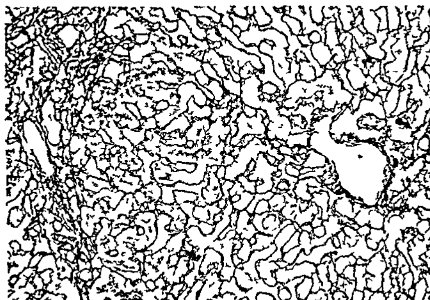


Fig 255 Same field as in Fig 254 showing preservation of normal reticulin structure Modified Foot s stain × 160



Fig 256—Same patient forty seventh day Fully developed hepatic cirrhosis Best's carmine stain × 90

Fig 257—Same field as in Fig 256 Reticulin stains confirm the disorganization of the normal hepatic lobular pattern Modified Foot's stain × 137

The absence of a history of previous jaundice does not exclude acute hepatitis in the past for mild attacks may well be passed over as intercurrent infections quickly forgotten and not related to the succeeding hepatic cirrhosis Bloomfield (1938) makes an interesting analogy between the natural histories of chronic hepatitis and chronic glomerulo nephritis Kelsall and others (1947) could find no difference between the clinical and pathological features of cirrhosis developing with no known cause and those of cirrhosis preceded by hepatitis There seems no doubt that post hepatitis cirrhosis and classical Laennec s cirrhosis can present the same clinical picture Future analysis of the effect of the great war time epidemics of hepatitis on the incidence of cirrhosis will enable the aetiological importance of hepatitis to be better assessed

(b) *Dietetic cirrhosis*

Interest in the dietetic production of liver lesions was initiated by the observation of MacLeod and his group (Allen and others 1924) in Toronto that pancreatecto mized dogs although maintained on insulin developed fatty change and cirrhosis in the liver This lesion could be prevented by choline Since that time much literature has arisen on the dietetic production of liver lesions Broadly speaking two types of hepatic pathology can be produced First massive hepatic necrosis and zonal necrosis which progresses to post necrotic scarring and secondly fatty infiltration of the liver and later fibrosis

Hepatic necrosis was produced in rats by a diet deficient in first-class protein and in particular sulphur containing amino acids (Himsworth and Glynn 1944) This lesion could be produced inconstantly in the hands of other workers and it was realized that a deficiency of factors other than amino acids might be present The necrogenic diet of Himsworth and Glynn was deficient also in α tocopherol (vitamin E) Tocopherol may compensate for absence of sulphur containing amino acids (cystine methionine) and vice versa Furthermore the liver lesion can be more readily produced if fat with a high content of unsaturated fatty acids (lard cod liver oil) is included in the diet As a further complication not only does the lack of cystine initiate the lesion but if excess of cystine is given production of the lesion is facilitated The aetiology of this type of hepatic necrosis has p obably not yet been clearly defined

Fatty infiltration and fibrosis is produced by a diet deficient in labile methyl groups (choline methionine) The fatty infiltration is related to disturbed phospholipid metabolism and occurs after about 14–21 days on the deficient diet The fibrosis which begins close to the central vein of the lobule appears after 70–100 days There are conflicting views about the relation of these two effects Himsworth and Glynn (1948) believe that the fatty change causes mechanical obstruction of the intralobular sinusoids and this is responsible for the eventual fibrosis Gyorgy and Goldblatt (1949) on the other hand believe that the two are quite unrelated and suggest that the continued mild cellular necrosis seen is a stimulus to fibroblastic proliferation The correct interpretation of these lesions is at present undecided Excellent reviews of the subject are given by Witts (1947) Gyorgy and Goldblatt (1949)

Application of these observations to disease in man is more difficult There seems no doubt that the high incidence of liver disease in under privileged peoples

can be related to dietetic deficiencies This is true for instance of the fatty livers and pigment cirrhosis of South African babies (Gillman and Gillman 1945) the malignant malnutrition (kwashiorkor) of children in Uganda (Trowell 1949) the fatty livers and cirrhosis of West Indian infants (Waterlow 1947) and the cirrhosis of the liver common among the poor natives of the Punjab (Hughes 1933) Certain diseases which interfere with the intake and metabolism of amino acids may be associated with dietetic liver lesions For instance a fatty liver is a practically constant association with chronic diarrhoea particularly in ulcerative colitis and this may progress to cirrhosis (Pollard and Block 1948) Patients with amino acid loss in the urine for instance the Fanconi syndrome may show fatty change in the liver and cirrhosis The relation of alcohol to hepatic cirrhosis will be discussed below Apart from these considerations it seems unlikely that the dietary intake of protein in Great Britain even in the poorest groups is so low as to result in liver injury and cirrhosis

(c) *Alcoholic cirrhosis*

Hepatic cirrhosis is 6 7 times as frequent in inebriates as in the temperate population (Joliffe and Jellinek 1941) However alcohol poisoning alone will not lead to cirrhosis (Joliffe and Jellinek 1941 Best and others 1949) and the relation between alcoholism and cirrhosis is probably indirect Most alcoholics take a poor general diet which is particularly deficient in protein and lipotropic factors At the same time their caloric intake in the form of alcohol is above normal An imbalance between caloric intake and the supply of essential food factors results and the consequent cirrhosis is dietetic and analogous to that described above in animals on experimental diets (Best and others 1949)

The choline requirement of the liver may well be related to caloric intake Cornatzer and Cayer (1950) have shown that there is probably diminished phospholipid synthesis and deficiency in labile methyl groups in alcoholic cirrhosis Using radioactive phosphorus the phospholipid turnover was shown to be at the lower limit of normal and large doses of methionine and choline considerably increased the turnover This type of cirrhosis could probably be prevented by ensuring that alcoholics took not only adequate calories (alcohol) but also essential amino acids and lipotropes (first-class protein)

(d) *Banti s syndrome (congestive splenomegaly)*

In 1898 Banti described a primary splenic di ease which was later followed by hepatic cirrhosis Three stages were recognized a pre ascitic in which the disease was confined to the spleen with leucopenia and microcytic hypochromic anaemia an intermediate with enlargement of the liver but with no hepatic symptoms and a third or ascitic stage with ascites liver failure and gastro intestinal haemorrhage However this clinical history is very rare In his wide experience Eppinger (1920) saw only one possible example McNee (1932) states that he never encountered a case history really showing the sequence of events originally described There are now grave doubts whether Banti s disease exists as a distinct entity It seems probable that this syndrome will result from a wide variety of conditions the common denominator of which is portal venous obstruction The lesion may be in the splenic veins in the portal veins (such as thrombosis

congenital occlusive bands cystic dilatation) or in the liver itself (most varieties of cirrhosis)

It is of interest that in cirrhosis the histological evidences of portal obstruction in the spleen do not correlate in extent with the hepatic fibrosis This latter may be minimal with conspicuous splenomegaly and portal hypertension (McMichael, 1934) A primary form of portal venous hypertension may also exist

The spleen in portal hypertension shows not only venous congestion but also cellular proliferation This represents one form of hypersplenism as defined by Doan and Wright (1946) and may account for the leucopenia and anaemia The cause of the cellular proliferation in the spleen is unknown but it suggests the presence of an additional cellular proliferating factor in portal hypertension (McMichael 1934) The anaemia can also be related to the gastro intestinal haemorrhages occurring in portal hypertension

In clinical medicine there is little useful purpose served by retaining the term Banti s syndrome which should be replaced by portal venous hypertension together with its cause

(2) Cardiac cirrhosis

In even mild cardiac failure there is dilatation of the central vein of the lobule

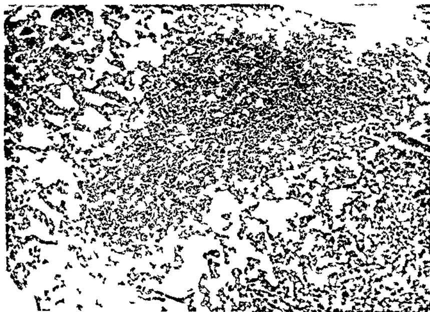


FIG 258—Cardiac failure Centrilobular haemorrhage and destruction of liver cells Adjoining sinusoids are dilated and peripheral liver cells show fatty change H 3 × 101

and the sinusoids entering it are engorged for a variable distance towards the periphery of the lobule (see Fig 258) In the more severe cases there is some centri lobular disappearance of liver cells The reticulin stroma collapses where the cells have disappeared The next stage is central reticulin proliferation Not only are

the reticulin fibres more closely packed together but there is *actual production of* new reticulin at the centre of the lobule The connective tissue extends outwards for a variable distance but does not reach the periphery of the lobule If the heart failure continues or relapses the connective tissue from one central vein joins that from the central veins of adjoining lobules The portal areas become surrounded by a ring of fibrous tissue passing from central vein to central vein This gives the appearance of reversed lobulation the portal tract apparently occupying the central position of the lobule This lesion is a frank cardiac cirrhosis (*see* Figs 259 and 260) The portal tracts may remain unaffected but in long standing cases they are often also involved the bile ducts proliferate fibroblasts are seen and sometimes there



FIG 259 —Cardiac cirrhosis Congestion in the centrilobular zones from which bands of fibrous tissue pass to adjoining central areas A portal tract occupies an apparently central position (reversed lobulation) H E 77

is also a little round celled proliferation When there are changes in both central areas and portal tracts a complex mixed picture results This may be difficult to distinguish from the classic portal cirrhosis If the heart failure continues or relapses the liver lesions progress If the heart failure is controlled then the acute hepatic changes disappear and the cardiac cirrhosis becomes latent and inactive and causes little hepatic functional disturbance (Sherlock 1951) Repeated episodes of failure are necessary for the development of full cardiac cirrhosis Patients with rheumatic mitral stenosis responding intermittently to treatment are therefore



Fig 60 —Same field as in Fig 259 Reticulin stains show the condensation and proliferation around the central veins from which bands pass to neighbouring central veins Portal tracts normal Modified Foot s stain × 80

particularly prone to develop cardiac cirrhosis If patients with other forms of heart failure survive for a sufficient length of time they too can develop the same cirrhosis Constrictive pericarditis with prolonged raised pressure and the hepatic venous system is also frequently associated with a cardiac type of cirrhosis

(3) **Haemochromatosis**

Iron in excess of immediate requirements cannot be excreted to any extent (McCance and Widdowson 1943) and is stored in the liver Both the cells of the reticulo-endothelial system (Kupffer cells) and the hepatic parenchyma take part in this storage The iron in excess is toxic to liver cells which disintegrate This occurs particularly in the periportal zones of the lobule where there is in addition a reactive fibrosis

In normal subjects excessive iron by mouth is not absorbed and it is impossible to produce hepatic cirrhosis in this way Multiple blood transfusions however with parenteral release of iron from effete red cells can readily lead to increased iron in the liver (Schwartz and Blumenthal 1948) Increased haemolysis and hence all forms of congenital and acquired haemolytic anaemia similarly result in excessive iron deposition in the liver Cirrhosis was also noticed in the livers of undernourished Germans after World War II In these subjects the iron release could be related to diminished blood volumes and low concentrations of haemoglobin Haemoglobin was therefore withdrawn from the circulation and

stored in the liver Release of myoglobin from muscle wasting may also have led to the liberation of iron (Sherlock and Walshe 1948) However in none of these conditions is the iron deposition of sufficient extent to provoke such liver cell disintegration and fibrosis as to warrant the term cirrhosis

In true haemochromatosis there are not only coarse granules of iron in the liver and reticulo endothelial cells but also gross fibrosis liver cell degeneration and disturbance of the lobular architecture The mechanism of this idiopathic haemochromatosis is uncertain Finch and others (1950) believe that the defect is one of excessive absorption of iron from the gastro intestinal tract whereas Fowler and Barer (1937) found the absorption of iron in this condition to be normal An alternative explanation is that the defect is an intracellular one and the iron accumulates in an abnormal form (Sheldon 1935) A somewhat similar explanation has been put forward for the interesting form of true haemochromatosis which occurs in South African pellagrins (Gillman and Gillman, 1945) The iron is said to originate from the mitochondria of the cell and to arise from a disturbance of intracellular metabolism due to dietetic imbalance This is an interesting speculation but in the absence of further data about the haemoglobin concentration and blood volume in these subjects it cannot be regarded as proved Moreover the iron seems in too great excess to have been derived only from the mitochondria

(4) Biliary cirrhosis

Obstruction to the common bile ducts leads to centrilobular accumulation of bile pigment often with bile stained focal necrosis of liver cells The portal tracts show bile duct proliferation fibrosis and scanty round celled infiltration As the biliary obstruction continues the fibrosis extends and increases passing from portal tract to portal tract so that the lobule is surrounded by a band of connective tissue (Fig 261) The essential lobular architecture however remains undisturbed and the lesion is not a true hepatic cirrhosis Liver cell regeneration does not occur in the presence of biliary stasis (Mann Fishbank Gay and Green 1931) If the biliary obstruction is incomplete, intermittent or surgical relief is possible then nodular hyperplasia of liver cells occurs and a true biliary cirrhosis results (Fig 262) Gall stones are the most frequent cause of intermittent biliary obstruction and of biliary cirrhosis

Biliary cirrhosis is sometimes encountered in patients without extrahepatic biliary obstruction and in whom the bile ducts are patent or even dilated (Dible McMichael and Sherlock 1947) The clinical features and laboratory findings are usually identical with those found in association with obstruction to the extrahepatic bile ducts The original description of the picture is usually ascribed to Hanot (1875) Watson and Hoffbauer (1946) called the disease cholangiolitic biliary cirrhosis and related it to a preceding infective hepatitis This relationship has been discussed in another chapter Thannhauser (1940) was particularly impressed by the associated skin xanthomas and the high serum cholesterol concentrations sometimes found in these patients He originally believed that the disease was a primary disorder of cholesterol metabolism with atheroma of the intrahepatic bile ducts causing obstruction to the outflow of bile Autopsy studies failed to reveal the expected biliary atheroma and the disturbed cholesterol metabolism is now thought to be secondary to the

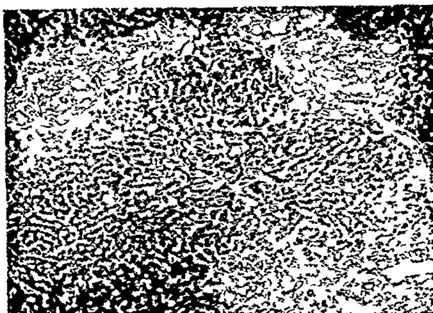


Fig. 261.—Unrelieved common bile-duct obstruction. Bile-duct proliferation and fibrosis in the portal tracts which are becoming joined together. Bile pigment accumulations at the lobular centre. Hepatic lobular architecture normal. H.E. × 67.5

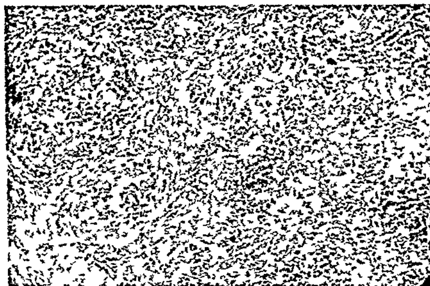


Fig. 262.—Biliary cirrhosis due to intermittent bile-duct obstruction. Note the disturbed lobular architecture. Bile thrombi stain darkly and are conspicuous adjoining the fibrous bands. H.E. × 60

biliary obstruction (MacMahon and Thannhauser 1949) There seems no doubt of the existence of this group of patients with intrahepatic obstructive jaundice The aetiology remains obscure the lesion is an obliteration of the intrahepatic bile ducts and an infective causation seems most likely

(5) Bilharzial cirrhosis

This condition is due to invasion of the liver by the eggs of *Bilharzia mansoni* The ova embolize in the portal vein from the intestines and are trapped in the portal tracts of the liver lobules A reaction is excited which includes fibrosis and inflammatory cell infiltration with necrosis of adjoining liver cells The lesion is a true hepatic cirrhosis Bilharzial cirrhosis is found particularly in Egypt Central and West Africa and South America

(6) Hepato lenticular degeneration (Kinnier Wilson s disease)

In 1912 Kinnier Wilson drew attention to the association of liver cirrhosis and degeneration of the central nervous system and in particular of the basal ganglia The hepatic lesion *corresponds to the general pattern of cirrhosis and histologically* cannot be distinguished from the usual portal variety

The aetiology of the condition is uncertain In erythroblastosis foetalis there is a liver lesion and also bile staining of the basal ganglia (kernicterus) and rhesus blood group incompatibility has been cited as the cause of Wilson s disease particularly as the condition is familial Studies on a large group of patients however have failed to show any relationship between the two diseases (Yannet and Lieberman 1946)

More interesting is the recent report of persistent amino aciduria in patients with Wilson s disease (Uzman and Denny Brown 1948) The excess in the urine has been quite clearly shown by paper chromatography (Dent 1949) Cooper and others (1950) have shown that the excretion of α amino nitrogen in the urine in six patients with Wilson s disease was more than twice that found in ordinary cirrhotics *They believe that there is a defect in renal function in Wilson s disease* with lowered renal threshold for amino acids The exact type of renal abnormality is unknown These findings suggest a link between Wilson s disease and the dietetic cirrhosis the excessive loss in the urine leading to deficiency of essential amino acids with necrosis and fibrosis in the liver

(7) Other postulated causes of cirrhosis

Chemical poisons

Acute carbon tetrachloride poisoning in man and experimental animals produces fatty infiltration of the liver In rats and dogs repeated administration of carbon tetrachloride over long periods is needed to result in hepatic cirrhosis (Bollman and Mann 1931 Cameron and Karunaratne 1936) It might be thought that in man also prolonged exposure to the substance would lead to cirrhosis However this does not seem to be the case and prolonged industrial exposure to carbon tetrachloride appears to promote resistance rather than susceptibility Investigation of a large series of workers using carbon tetrachloride failed to show a single case of cirrhosis due to the vapour (Smyth and Smyth 1936) It appears that carbon tetrachloride is not an important aetiological factor in cirrhosis This

applies also to the related substances chloroform and tetrachlorethane

Arsenical poisoning has been reported with cirrhosis in man but is a rarity and arsenic intoxication is not an important cause of cirrhosis The association of cirrhosis in syphilitics having had previous organic arsenical therapy is probably through a preceding serum hepatitis resulting from contaminated syringes

Syphilis

Syphilis was formerly considered an important factor in the production of hepatic cirrhosis This is apparently not so in adults although in congenital syphilitic infants invasion of the liver by the spirochaetes does result in pericellular fibrosis and cirrhosis In adults the only lesion clearly related to syphilis is the gumma which on healing leaves a scar These scars may result in a coarsely nodular liver (hepar lobatum) but are never so widespread as to merit the term cirrhosis It seems more likely that cirrhosis discovered in previously treated syphilitics is in fact related to a previous serum hepatitis The opportunity for syringe trans mission of hepatitis in patients attending venereal disease clinics is well known

Malaria

Malarial parasites cause a reaction in the reticulo endothelial system generally and hence proliferations both of the Kupffer cells of the hepatic sinusoids and the large macrophages of the portal tracts The destruction of red blood cells leads to release of bilirubin which further stimulates reticulo-endothelial proliferation If severe the anaemia and fever are associated with centrilobular liver cell necrosis These features however do not result in chronic diffuse liver disease with fibrosis and destruction of the hepatic lobular architecture and malaria is of no importance in the aetiology of cirrhosis The frequent occurrence of malaria and cirrhosis in the same patient must be ascribed to malaria and conditions causing cirrhosis (for example bilharziasis malnutrition) being simultaneously present in the community

CLINICAL AND LABORATORY FEATURES OF CIRRHOSIS

Although the various types of cirrhosis have certain individual characteristics the effects of the lesion are common and can be divided into two main groups First there are those related to changes in the intrahepatic vasculature with consequent portal venous hypertension The second group results from the func tional inadequacy of the hepatic cells The clinical investigation of a patient suffering from any type of cirrhosis involves an assessment of the part played by each of these major factors In the case of biliary cirrhosis a further consideration is the obstruction to the biliary system The following account refers to classic portal or Laennec s cirrhosis which is used as a type example The differential diagnostic features of the other varieties of cirrhosis will be described later

PORTAL VENOUS HYPERTENSION AND THE CIRCULATION IN CIRRHOSIS

The liver receives a double blood supply The portal venous pressure is low but the portal vein supplies 75 per cent of the total hepatic blood flow the blood having a low oxygen content The hepatic artery has a high blood pressure but supplies only 25 per cent of the hepatic flow The hepatic arterial blood of course

has a high oxygen content There is no conclusive evidence of direct arterio venous anastomoses between the two supplies Communication occurs in the sinusoids at the periphery of the hepatic lobule into which the tributaries of portal vein and branches of the hepatic artery enter In cirrhosis there is simplification reduction and distortion of both hepatic arterial and portal venous radicals (McIndoe 1928) Portal venous pressure rises because of the intrahepatic portal venous obstruction Another factor is the transmission of hepatic arterial pressure to the portal venous system due to the intrahepatic vascular distortion (Herrick 1907 Dock 1947) The hepatic parenchyma comes to rely more and more for its nutrition on the hepatic arterial supply

It is difficult to estimate hepatic blood flow in man and in particular the proportions supplied by hepatic arterial and portal venous components Using a catheter passed under fluoroscopic control *via* an antecubital vein through the right auricle into a branch of the hepatic vein Bradley and others (1945) estimated the total hepatic blood flow in man to be of the order of 1 500 millilitres per minute In portal cirrhosis the flow was usually reduced to about 900 millilitres per minute (Bradley 1949) The oxygen consumption of the liver was maintained in these cirrhotic subjects by a greater extraction of oxygen by surviving liver cells in spite of the reduced blood flow Myers (1950) by an ingenious method involving not only hepatic venous catheterization but also sampling of a portal collateral vein on the anterior abdominal wall estimated the proportions of the hepatic blood flow derived from the portal vein and hepatic artery In two patients with small cirrhotic livers the portal venous flow was estimated at about 75 per cent of the total whereas in one patient with an enlarged cirrhotic liver the hepatic artery contributed 75 per cent These results are preliminary and future developments along these lines will be awaited with great interest The hepatic venous catheterization technique for the estimation of splanchnic blood flow involves the continuous infusion of bromsulphalein It is therefore confined to those patients without jaundice in whom liver dysfunction is minimal and its use in the study of cirrhosis is limited

The portal vein remains inaccessible to the clinical investigator and there is great difficulty in estimating the portal circulation time or venous pressure Newman and Cohen (1949) measured the portal circulation time in man by the insufflation of ether into the rectum The time for the vapour to be smelt in the breath was taken Patients with cirrhosis showed a significant increase in this time indicating the portal venous obstruction

The pressure in a portal collateral vein on the abdominal wall bears a good relationship to the direct portal venous pressure estimated at operation The observed pressure in such a vein is the algebraic sum of the positive portal venous pressure and the negative intrathoracic pressure and when using this technique care must be taken to exclude this latter factor by manual compression of the vein proximal to the point of measurement (Davidson Gibbons and Faloon 1950)

Patients with a severe decompensated hepatic cirrhosis often show a hyper dynamic circulatory state There is peripheral vasodilation with warm extremities and a large pulse pressure the cardiac output is increased This observation may be linked with that of Shorr (1947) that the anoxic liver manufactures a vasodilatory material (V D M) This substance is also normally inactivated by

the liver and accumulates in decompensated cirrhosis V D M *has been identified* chemically with ferritin (Mazur and Shorr 1948)

Attention should be paid in the clinical history to haematemesis which may *come not only from oesophageal varicosities* but also *from dilated veins in the* stomach wall Bleeding from haemorrhoids must also be noted The anterior abdominal wall should be carefully examined for distended veins a frank caput *medusae is rare and usually only 1 or 2 veins are noted running from the umbilical* region The blood flow in these veins is radially away from the umbilicus This is in contra distinction to collaterals occurring with inferior vena caval obstruction in which the blood flow is always upwards over the abdominal wall Tense ascites leads to functional obstruction of the inferior vena cava and may cause difficulty in the interpretation of anterior abdominal wall veins The use of infra red photography to show up the veins more clearly is to be recommended and clinically they may be more easily seen by red goggles such as those used by radiologists As a further diagnostic aid a glucose drink may be given and 30 minutes later the glucose content of the blood in the anterior abdominal wall vein and in an antecubital vein estimated A higher glucose content in the abdominal than in the antecubital vein confirms that the abdominal vein is a portal collateral (Sherlock and Walshe 1946) Occasionally in cirrhosis the anastomotic umbilical vein may be so dilated that a venous hum can be heard above and to the right of the *umbilicus (Cruveilhier–Baumgarten syndrome) (Bloom 1950) The size of the* spleen in cirrhosis is another indication of portal hypertension Portal obstruction is also one factor in the production of ascites and this will be discussed later Oesophageal varicosities *can often be demonstrated radiologically using a thick* barium emulsion Oesophagoscopy is rarely indicated Proctoscopy is used to visualize haemorrhoids Portal hypertension is discussed more fully in Chapter 32

ASSESSMENT OF HEPATIC CELLULAR FUNCTION

Changes in bile pigment metabolism

Jaundice in a cirrhotic patient means that the rate of destruction of liver cells has exceeded the capacity for regeneration and the lesion is a decompensated one It is therefore of serious consequence and considerably worsens the prognosis Icterus is rarely deep serum bilirubin values being of the order of 2–5 milligrams per 100 millilitres *In general the deeper the jaundice the greater the inadequacy* of the liver cell function Sometimes icterus is precipitated by an acute episode of liver damage such as an alcoholic bout or an intercurrent infection In these patients jaundice is *not so serious and may well disappear if the acute condition* can be treated An increase in the serum bilirubin value in cirrhosis is by no means constant and many patients with well compensated hepatic lesions have serum bilirubin values of less than 1 0 milligram per 100 millilitres

The qualitative van den Bergh reaction and the proportions of the serum bilirubin acting *directly* and *indirectly* with the diazo reagent are non contributory in the clinical investigation of cirrhosis

The bromsulphalein excretion test is a further sensitive method of estimating liver cell *function (Helm and Machella 1942) Bromsulphalein* is *probably* metabolized in a similar fashion to bilirubin and its retention in the blood stream

after intravenous injection reflects an inability of the liver to excrete bile pigment It is clearly of no value in patients with raised serum bilirubin concentrations in whom there is already a clear indication of inability to excrete naturally formed bilirubin

Excess of urinary urobilinogen or its oxidation product urobilin further indicates failure of liver cell function Urobilinogen is normally absorbed from the intestines and re excreted by the liver into the bile If liver cell function fails some of this urobilinogen is excreted by the kidneys into the urine Qualitative tests are simply performed either for urobilinogen by Ehrlich s aldehyde reaction or for urobilin by Schlesinger s alcoholic zinc acetate method Daily urine testing for these substances often gives as good an evaluation of the state of the liver cells in cirrhosis as far more time consuming laboratory procedures

Of more academic interest is the finding of increased isomeric Type I copro porphyrin in the urine of patients with cirrhosis developing after infective hepatitis The urine of patients with alcoholic cirrhosis has been shown to contain excess of the Type III coproporphyrin isomer (Watson and Larson 1947) This indicates a specific difference in porphyrin metabolism in the two types of cirrhosis

Bilirubin appears in the urine only when the patient is frankly jaundiced

Changes in protein metabolism

It is generally accepted that the liver plays a major role in the regeneration of the plasma proteins (Madden and Whipple 1940) This is particularly true of the plasma albumin Some plasma globulin may be formed elsewhere (Sabin 1939) Chronic diffuse liver disease therefore results in a diminished plasma albumin level and this is partially compensated by an increase in the plasma globulin In general the lower the plasma albumin the greater the extent of hepatic cell necrosis and the worse the prognosis (Sherlock 1946b)

In active cirrhosis not only are the plasma proteins quantitatively abnormal but there is a change in their constitution as shown by electrophoretic analysis (Gray and Barron 1943)

The serum albumin content is diminished and there is an increase in the γ globulin with smaller increases in the α and β globulins (Whitman and others 1950) This results in positive findings for various flocculation and precipitation tests A positive thymol turbidity (Maclagan 1944) is mainly dependent on changes in the globulin and probably indicates continuing inflammatory cell change in the liver A positive colloidal gold reaction (Gray 1940) or zinc sulphate test (Kunkel 1948) is dependent mainly on changes in the β globulin component of the serum and is positive particularly with liver cell degeneration especially with fatty change It follows that the thymol turbidity test should be more often po itive in post hepatitis cirrhosis whereas a positive colloidal gold reaction or zinc sulphate test is usually associated with the nutritional alcoholic cirrhosis In practice results for the two tests in cirrhosis usually run in parallel

Estimation of the plasma albumin and plasma globulin values and performance of two precipitation tests are useful adjuncts in the diagnosis of cirrhosis and in assessing the progress of the patient It must be emphasized however that normal results can occur for all these procedures although the patient has a definite cirrhosis Electrophoretic studies of the serum may also give normal results in well compensated cirrhosis (Ricketts Sterling Kirsner and Palmer 1949)

Ascites in cirrhosis

In the dog portal venous hypertension is not an essential factor for the formation of ascites (Volwiler Grindlay and Bollman 1950) In man also an increased portal venous pressure although a measurable factor cannot alone account for the formation and maintenance of ascites or oedema in patients with cirrhosis (Davidson and others 1950 Pattison 1949)

Reduction of the colloid osmotic pressure of the plasma consequent upon the failure of the liver to maintain the plasma-albumin concentration assists transudation of fluid from the capillaries into the peritoneal cavity but it is also doubtful whether this factor alone ever initiates ascites in cirrhosis However the two factors of portal hypertension plus hypoproteinaemia in the dog will produce ascites of a thin watery type with a low protein content (Volwiler and others 1950)—a fluid very similar in type to that found in the peritoneal cavity in human cirrhosis

These are not the only factors involved in ascites in man Patek and others (1948) gave intravenous injections of concentrated human serum albumin to patients with cirrhosis and ascites There was an increase in the albumin concentration in the ascitic fluid This suggests that the portal vascular bed is unduly permeable in these patients

Once ascites has developed its continuation is perpetuated by disturbed sodium metabolism The ascites is formed out of proportion to available sodium and there is compensatory dilution of body fluids Serum sodium values are low as is the sodium concentration of urine sweat and saliva (Eisenmenger and others 1950) These results suggest that there is a generalized disturbance of sodium metabolism A hormonal mechanism may be involved possibly related to adrenal cortical hyperplasia There are elevated reducing corticoids in the urine of most patients with cirrhosis and these have been identified with the adrenal salt and water hormones (Eisenmenger and others 1950) In view of these findings a specific renal change with respect to sodium metabolism in cirrhosis as postulated by Goodyer and others (1950) does not seem likely

Yet another factor in the production and perpetuation of ascites is the finding of increased anti-diuretic activity in the urine in patients with ascites and cirrhosis The anti-diuretic substance involved is probably not inactivated by the damaged liver (Ralli and others 1945) Originally the anti-diuretic substance was identified with the hormone from the posterior lobe of the pituitary A more recent suggestion is that the substance is identical with the vasodilator material (V D M) of Shorr (1947)

Ascites raises the intra abdominal pressure and renal blood flow is reduced (Bradley and Bradley 1947) This is a further renal factor present in cirrhosis tending to retain fluid in the tissues

The aetiology of ascites in cirrhosis is therefore complex Its presence implies that factors additional to portal hypertension are operating and in general it is indicative of liver parenchymal inadequacy

Changes in carbohydrate metabolism

The liver is the keystone of carbohydrate metabolism Ingested glucose reaches the liver by the portal vein and is there stored to be released to the blood stream

as required for the maintenance of the blood glucose concentration The liver also converts the monosaccharides fructose and galactose to glucose Abnormalities in the glucose laevulose and galactose tolerance tests might be expected in patients with cirrhosis However, the reserve power of the liver with respect to carbo hydrate metabolism is so great that very severe liver cell damage is necessary before these tests become positive and carbohydrate tolerance tests are of little practical importance in the study of cirrhosis Similarly the cirrhotic liver might not be able to maintain a normal blood glucose value Hypoglycaemic episodes do occur in the cirrhotic patient but are infrequent

Changes in cholesterol metabolism

The liver excretes cholesterol in the bile and obstructive lesions of the biliary passages may be associated with a raised total serum cholesterol concentration The hepatic parenchyma also esterifies cholesterol with fatty acids The sera of active cirrhotics show a diminished proportion of esterified to free cholesterol and this ratio is an excellent index of hepatic cellular function Unfortunately the use of this procedure is usually impracticable because of the tedious nature of the chemical estimation The serum lipids in liver disease have recently been discussed by Man and others (1945)

Haematological changes

Most textbooks describe a macrocytic anaemia associated with cirrhosis This is related to failure of the liver to synthesize and store the anti pernicious anaemia principle However recent bone marrow studies do not support this concept as erythropoiesis is usually macro normoblastic and not megaloblastic (Berman and others 1949) The anaemia is probably relative and is due to a marked increase in total blood volume with a relatively greater increase in plasma than circulating red cell mass this suggests a more severe anaemia than actually exists (Bateman Shorr and Elgvin 1949) Anaemia in cirrhosis also results from alimentary tract blood loss related to portal venous hypertension iron deficiency from poor dietary habits and disturbed haemoglobin metabolism from failure of proper protein synthesis in the liver

The bleeding tendency in cirrhosis is usually attributed to inadequate pro thrombin manufacture by the diseased liver and in general a prolonged prothrombin time in cirrhosis is a good reflection of severe liver cell damage Thrombocytopenia may contribute to the bleeding tendency (Morlock and Hall 1943)

Detoxication changes

Poisons enter the body through the gastro intestinal tract and pass *via* the portal venous system to the liver A cirrhotic liver detoxicates poisons less well than normal and this leads among other things to poor tolerance for morphine and barbiturate drugs which should be exhibited cautiously This applies particularly to the short acting barbiturate anaesthetics which are safe only in small doses and should only be used for inducing anaesthesia

Some liver function tests are based on the detoxicating power of the liver The most popular utilizes the conjugation by the liver of benzoic acid with glycine to form hippuric acid Patients with active cirrhosis usually show an impaired hippuric

acid synthesis test but this test has proved of little practical value as it is so often positive in non hepatic conditions and bears little relation to underlying changes in the liver (Sherlock 1945)

The liver is the essential organ for the inactivation of oestrogens and other steroids and this may be the explanation of certain endocrine changes in cirrhosis These are well reviewed by Lloyd and Williams (1948) In males loss of body hair gynaecomastia and testicular atrophy may occur In females changes in the menstrual pattern in body hair and atrophy of breasts and uterus are noted Certain cutaneous lesions which occur both in cirrhotics and in pregnant women are attributed to excess of circulatory oestrogens These include vascular spiders and palmar erythema Cutaneous arterial spiders are found only in the vascular territory of the superior vena cava They consist of a central point which may be raised and in which pulsation is sometimes seen Branching vessels radiate from the centre Pressure of the centre with a pin head leads to blanching of the entire lesion (Bean 1945) The palmar erythema is seen over the pads of the fingers and over the thenar and hypothenar eminences The surface is red and mottled with increased temperature The soles of the feet may be similarly affected

It is by no means certain that these changes are due to oestrogen excess Dohan and others (1950) have measured the urinary excretion of free and conjugated portions of oestrone oestradiol and oestriol in patients with cirrhosis They could find no correlation between the results and the severity of the liver disease or with gynaecomastia vascular spiders and testicular atrophy The 17 ketosteroid output was moderately decreased in the patients with the most severe chronic liver disease Part of this diminution however may have been due to the greater age of this group and to the non specific effects of prolonged illness Whatever the eventual explanation of these endocrine changes however all of them are indicative of inadequacy of liver cell function

Aspiration liver biopsy and cirrhosis

The patient presenting the full picture of decompensated liver disease does not require an aspiration liver biopsy to confirm the diagnosis However a high proportion of patients with cirrhosis remain compensated and have equivocal clinical features and normal biochemical tests Scrutiny of the last 50 case histories of patients with cirrhosis seen at the Postgraduate Medical School of London shows that in 25 there was doubt in the clinical diagnosis In all these patients liver function tests were non contributory but in 24 a correct diagnosis could be made with the aid of the aspiration liver biopsy sections There are certain draw backs to the use of the technique in the cirrhotic subject If ascites is present the liver may be ballotable and difficult to fix paracentesis should be performed be fore the puncture is attempted Failure may also result if the liver is very tough and difficult to pierce a few liver cells may then be extracted leaving the fibrous framework behind (Sherlock 1946a) Particular care should also be taken if it is suspected that the liver has greatly contracted as there is a chance of the biopsy trocar missing the liver and perforating a hollow viscus such as the gall bladder However suspected cirrhosis still remains one of the important indications for aspiration liver biopsy and in the great proportion of cases gives

as required for the maintenance of the blood glucose concentration The liver also converts the monosaccharides fructose and galactose to glucose Abnormalities in the glucose laevulose and galactose tolerance tests might be expected in patients with cirrhosis However the reserve *power of the liver with respect to carbo* hydrate metabolism is so great that very severe liver cell damage is necessary before these tests become positive and carbohydrate tolerance tests are of little *practical importance in the study* of cirrhosis Similarly the cirrhotic liver might not be able to maintain a normal blood glucose value Hypoglycaemic episodes do occur in the cirrhotic patient but are infrequent

Changes in cholesterol metabolism

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and a return to a compensated state If the liver cell failure is related to an acute alcoholic episode recovery of function may follow abstinence and in general all patients with cirrhosis should become total abstainers Where there is no apparent cause for the failure or when the cause has been treated the management of the patient must be on more general lines

Bed rest is essential and should be continued while improvement is maintained The work of Patek and others (1941) showing the advantages of a nutritious diet in the treatment of cirrhosis was a landmark in this field Their present regime includes a 3 500 caloric diet containing 140 grams protein 175 grams fat and 465 grams carbohydrate with 50 grams powdered brewer s yeast (Patek and others 1948) The need of such a liberal diet may be questioned Klatskin and Yesner (1949) studied a group of 14 cirrhotics most of them alcoholic When put to bed deprived of alcohol and given a diet containing only 1 gram of protein and 30 calories per kilogram body weight these subjects showed clinical functional and hepatic histological improvement This protein deprivation in the treatment of cirrhosis however when carried to extremes may slow recovery Eckhardt and others (1950) gave a group of three cirrhotics no protein but adequate calories Although there was clinical improvement and improvement also in the biochemical tests of liver function the nitrogen balance continued to be negative and the hepatic histological picture was unchanged Increased protein fe ding resulted in a positive nitrogen balance and aspiration biopsy studies showed a disappearance of fat from the liver cells and a recovery of liver cell protein A reasonable regime seems to be a diet containing about 2 500 calories with 100 grams protein Fat need not be restricted within the caloric total Fresh brewer s yeast if tolerated can be given in one dessertspoon doses stirred in milk 3 times a day This provides additional first-class protein and also the vitamin B complex. The addition of methionine and choline is said to be of value (Beams 1946 Russakoff and Blumberg 1944 Franklin and others 1948) These reports have very inadequate control groups and the work was performed before the advantages to be obtained from b d rest and alcohol abstinence were fully realized A group of 228 cirrhotics studied by Wade and others (1948) with 311 controls showed that the addition of choline and skimmed milk as a source of methionine failed to influence the rate of recovery in cirrhosis These supplements are not indicated in the ordinary patient with hepatic cirrhosis Moreover in the severely ill subject they are probably not utilized *This was well demonstrated by Kinsell and others (1950) who gave* methionine in which the sulphur was radioactive (S^{3}) to cirrhotic patients Compared with normal subjects the cirrhotic patient had difficulty in incorporating the methionine into the plasma proteins thus indicating impairment of plasma protein metabolism Gabuzda and others (1950) had also shown that choline and methionine will not increase nitrogen storage in cirrhosis

Liver extract given intravenously in large dos s has also been shown to be of benefit Of 68 patients treated in this way 48 per cent were alive at the end of 3 years whereas of 44 conventionally treated controls only 12 per cent survived 3 years (Ralli and others 1949) The differences however are much less conspicuous than is at once apparent for the control group was not run concurrently with the test but was studied earlier at a time when blood transfusion and chemo therapy to treat the haemorrhage and intercurrent infections of cirrhosis were

an accurate diagnosis and enables the activity of the lesion to be assessed Serial aspiration hepatic biopsies may be used to follow progress and to evaluate the therapy instituted

Diagnosis of the type of cirrhosis

As has already been indicated the investigation of all patients suspected of suffering from cirrhosis involves an evaluation of the liver cellular function and the degree of portal venous hypertension The cirrhosis associated with different aetiological factors may present additional diagnostic features

Classic portal or Laennec s cirrhosis has been used as the type example and has been discussed fully above The importance of alcoholism and of infective hepatitis in the preceding history may again be emphasized

Wilson s disease or hepato lenticular degeneration is recognized by its familial nature and by the associated neurological signs of basal ganglia degeneration Slit lamp study may show the characteristic golden yellow pigment rings in the cornea (Kayser–Fleischer rings) Liver cell failure or portal hypertension is rare

Patients with haemochromatosis may have skin pigmentation and endocrine disturbances particularly gonadal atrophy and diabetes Exact diagnosis involves the demonstration of excess iron in the tissues In the skin it is shown by biopsy or the ferricyanide intradermal test (Beardwood and Rouse 1944) in the liver by aspiration biopsy or in the urine by iron staining of the centrifuged deposit The liver lesion in haemochromatosis is usually compensated and portal hypertension jaundice and ascites are rare

Cardiac cirrhosis usually has no specific clinical or biochemical associations It does not produce portal venous hypertension and jaundice in patients with heart failure does not necessarily indicate cardiac cirrhosis (Sherlock 1951) Cardiac cirrhosis can occur with all the aetiological forms of heart failure but is most frequent in patients with mitral stenosis and tricuspid valvular incompetence in whom congestive failure is intermittent and prolonged Bilharzial cirrhosis is recognized by its geographical distribution It results in portal hypertension without much hepatic parenchymal dysfunction Aspiration liver biopsy may demonstrate the ova of the parasite in the portal tracts

Biliary cirrhosis is usually associated with clinical manifestations of the causative lesion This is frequently gall stones and there is usually some systemic infection with mild fever leucocytosis and raised erythrocyte sedimentation rate Jaundice is fluctuant Ascites and portal hypertension are terminal The biochemical findings are those of obstructive jaundice with an increased serum alkaline phosphatase and cholesterol and normal plasma proteins and flocculation tests Aspiration liver biopsy may be diagnostic but in a phase where jaundice is minimal and intra hepatic bile pigment retention slight the histological appearances can be very difficult to distinguish from those of portal cirrhosis

TREATMENT OF CIRRHOSIS

The treatment of cirrhosis with liver cell failure is very disappointing The best results occur when the failure has a very clear precipitating cause Thus an acute infection may respond to antibiotics and the anaemia of gastro intestinal haemor rhage be relieved by blood transfusion with consequent liver cell regeneration

and a return to a compensated state If the liver cell failure is related to an acute alcoholic episode recovery of function may follow abstinence and in general all patients with cirrhosis should become total abstainers Where there is no apparent cause for the failure or when the cause has been treated the management of the patient must be on more general lines

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not so generally available as they are at present Liver extract is difficult to prepare for intravenous use and is not at present commercially available in this country

Aureomycin when added to a necrogenic yeast diet will delay the development of experimental hepatic necrosis in rats The aureomycin might act through the suppression of the intestinal bacterial flora (Gyorgy and others 1950) However aureomycin given to 13 patients with chronic liver disease produced benefit in only 7 Positive evidence for the value of aureomycin is therefore only suggestive and a further study is needed to determine the validity of the impressions obtained from this small group (Shaffer and others 1950)

Adrenocorticotrophic hormone (ACTH) has been used in the treatment of cirrhosis (Bongiovanni Eisenmenger and Kunkel 1950) In three patients with biliary cirrhosis or severe alcoholic cirrhosis with ascites ACTH produced no significant improvement Four young women with a cirrhosis of undetermined aetiology showed a diminution in serum bilirubin concentration and an increased albumin synthesis when given ACTH and this persisted for about 6 weeks after cessation of therapy There were conspicuous side reactions in four of the severely ill patients Two showed a bloody ascites and two an elevation of the fasting blood glucose level to over 250 milligrams per 100 millilitres This latter returned to normal with 24 hours of stopping the drug It is obvious that ACTH has variable effects in cirrhosis and experience at the present time is too limited for its value to be accurately assessed

Ascites modifies the treatment Paracentesis abdominis is only palliative and results in great loss of body proteins Measures must be taken to prevent the fluid re accumulating and of these the most helpful is the restriction of the dietary sodium chloride intake (Eisenmenger and others 1949) A cirrhotic patient who is accumulating ascites can by both renal and extrarenal channels excrete only 1 5 grams sodium chloride daily Every gram of sodium chloride taken above this amount means that 100 millilitres water will be retained in the tissues Sodium chloride intake should therefore not exceed 1 gram daily It may be difficult to maintain the protein content of such a diet without the use of low salt content bread and low sodium milk powder Ion exchange resins may eventually prove the answer to the problem The patient can then take a diet of normal sodium content and the sodium will be taken up on to the resin and not absorbed Mercurial diuretics may also be useful in the prevention of further ascites Human salt poor albumin infusions have been used to raise the serum colloidal osmotic pressure but are of only transitory value and untoward reactions to them have been reported (Davidson and others 1950)

The treatment of portal venous hypertension is largely surgical and is chiefly concerned with anastomosis of the portal and systemic venous systems In cirrhosis there is already intrahepatic obstruction to the portal vascular bed and further diversion of portal blood into the systemic veins is not attended by any serious effects on the liver cells Most patients with alcoholic cirrhosis have disturbed liver cell function and candidates for porta caval anastomoses are usually found in the group of younger subjects with post hepatitis cirrhosis In these patients normal liver cell function may exist with gross portal venous hypertension

The treatment of bleeding oesophageal or gastric varices depends on the severity of the haemorrhage A small ooze may stop spontaneously with or without blood

transfusion Severe haemorrhage can sometimes be checked by the introduction of a balloon into the stomach which after inflation is drawn up against the cardia by means of traction on the rubber tube to which the balloon is attached (Rowntree and others 1947) Porta caval anastomoses performed as a surgical emergency to relieve portal pressure and stop haemorrhage are fraught with considerable hazard (Linton 1949) The injection of oesophageal varicosities through an oesophagoscope is rarely attempted nowadays The danger of full doses of morphine to cirrhotic patients with bleeding oesophageal varicosities must be emphasized

REFERENCES

Allen F N Bowie D J Macleod J J R and Robinson W L (1934) *B it J exp Path* 5 75

Baez S Mazur A and Shorr E (1950) *Amer J Phys* 162 198

Bateman J C Shorr H M and Elgvin T (1949) *J clin Invest* 28 539

Beams A J (1946) *J Amer Med Ass* 130 190

Bean W B (1945) *Medicine* 24 243

Beardwood J T Jun and Rouse G P Jun (1941) *Clinics* 3 251

Berman L Axelrod A R Horan T N Jacobson S D Sharp E A and Vonder Heide E C (1949) *Blood* 4 511

Best C H Hartroft W S Lucas C C and Ridout J H (1949) *Brit med J* 2 1001

Bloom H J G (1950) *B it heart J* 12 343

Bloomfield A L (1938) *Amer J Med Sci* 195 429

Bollman J L and Mann F C (1931) *Ann intern Med* 5 699

Bongiovanni S H Eisenmenger W J and Kunkel H G (1950) *J clin Invest* 29 796

Bradley S E and Bradley G P (1947) *Ibid* 26 1010

— Ingelfinger F J Bradley G P and Curry J J (1945) *Ibid* 28 890

— (1949) *New Eng Med J* 240 456

Cameron G R and Karunaratne W A E (1936) *J Path Bact* 42 1

Cooper A M Eckhardt R D Faloon W W and Davidson C S (1950) *J clin Invest* 29 265

Cornatzer W E and Cayer D (1950) *Ibid* 29 54

Davidson C S Gibbons T B and Faloon W W (1950) *J Lab clin Med* 35 181

Dent C E (1949) *Biochem Soc Symposie No* 3 London Cambridge University Press

Dible J H McMichael J and Sherlock S (1947) *Gastroenterologia* 9 736

Doan C A and Wright C S (1946) *Blood* 1 10

Dock W (1947) *New Engl J Med* 236 773

Dohan F Richardson E M Bluemle L and Gyorgy P (1950) *J clin Invest* 29 808

Eckhardt R D Zamcheck N Sidman R L Gabuzda G J and Davidson C S (1950) *Ibid* 29 27

Eisenmenger W J Blondheim S H Bongiovanni A M and Kunkel H G (1950) *Ibid* 29 149

— Ahrens E J Jun Blondheim S H and Kunkel H G (1949) *J Lab clin Med* 34 1029

Eppinger H (1920) *Die Hepato lienalen Erkrankungen* Berlin Springer

Finch C A Hegsted M Kinney T D Thomas E D Rath C E Haskins D Finch, S and Fluharty R G (1950) *Blood* 5 983

Fowler W M and Barer A P (1937) *J Lab clin Med* 23 47

Franklin M Salk M R Steigmann F and Popper H (1948) *Amer J clin Path* 18 273

Gabuzda G J Jun Eckhardt R D and David on C S (1950) *J clin Invest* 29 566

Gillman J and Gillman T (1945) *Arch Path* 40 239

Goodyer A V N Redman A S Lawrason F D and Epstein F H (1950) *J clin Invest* 29 973

Gray S J (1940) *Arch intern Med* 65 524
— and Barron E S G (1943) *J clin Invest* 22 191
Gyorgy P Stokes J Jun Smith W H and Goldblatt H (1950) *Amer J med Sci* 220 6
— and Goldblatt H (1949) *J exp Med* 89 245
Hanot V (1875) Sur une forme de cirrhose hypertrophique *Thèse de Paris*
Helm J D and Machella T E (1942) *Amer J digest Dis* 9 141
Herrick F C (1907) *J exp Med* 9 93
Himsworth H P (1948) *Science Progress* 36 577
— and Glynn L E (1944) *Clin Sci* 5 93
— (1948) *Ibid* 6 235
Howard R and Watson C J (1947) *Arch intern Med* 80 1
Hughes T A (1933) *Indian J med Res* 21 353
Joliffe N and Jellinek E M (1941) *Quart J Stud Alcohol* 2 544
Jones C M and Minot G R (1923) *Boston med surg J* 189 531
Kelsall A R Stewart A and Witts L J (1947) *Lancet* 2 195
Kinsell L W Margen S Tarver H Frantz J McB Flanagan E K Hutchin M E Michaels G D and McCallie D P (1950) *J clin Invest* 29 238
Klatskin G and Yesner R (1949) *Ibid* 28 723
Kunkel H G Andrews E H Jun and Eisenmenger W G (1948) *Gastroenterology* 11 499
Linton R R (1949) *Ann intern Med* 31 794
Lloyd C W and Williams R H (1948) *Amer J Med* 4 315
McCance R A and Widdowson E M (1943) *Nature Lond* 152 326
McIndoe A H (1928) *Arch Path* 5 23
Maclagan N F (1944) *Brit J exp Path* 25 234
MacMahon H E and Thannhauser S J (1949) *Ann intern Med* 30 121
McMichael J (1934) *J Path Bact* 89 481
McNee J W (1932) *Brit med J* 1 1111
Madden S C and Whipple G H (1940) *Physiol Rev* 20 194
Man E B Kartin B L Durlacher S H and Peters J P (1945) *J clin Invest* 24 623
Mann F C Fishbank F C Gay J G and Green G F (1931) *Arch Path* 12 797
Mazur A and Shorr E (1948) *J Biol Chem* 176 771
Moon V H (1932) *Arch path* 13 691
Morlock C G and Hall B E (1943) *Arch intern Med* 72 69
Myers J D (1950) *J clin Invest* 29 836
Newman H F and Cohen I B (1949) *J lab and Clin Med* 34 674
Patek A J Jun Mankin H Colcher H Lowell A and Earle D P Jun (1948) *J clin Invest* 27 135
— and Post J (1941) *Ibid* 20 481
Pattison A C (1949) *Arch Surg* 58 590
Pollard H M and Block M (1948) *Arch intern Med* 82 159
Ralli F P Leslie S H Stueck G H Jun Shorr H E Robson J S Clarke D H and Laken B (1949) *Medicine* 28 301
— Robson J S Clarke D H and Hoagland C L (1945) *J clin Invest* 24 316
Ratnoff O D and Patek A J Jun (1942) *Medicine* 21 207
Rennie J B (1945) *Amer J med Sci* 210 18
Ricketts W E Sterling K Kirsner J B and Palmer W L (1949) *Gastroenterology* 13 205
Rowntree L G Zimmerman E F Todd M H and Ajac J (1947) *J Amer med Ass* 135 630
Russakoff A H and Blumberg H (1944) *Ann intern Med* 21 848
Sabin F R (1939) *J exp Med* 70 67
Schwartz S O and Blumenthal S A (1948) *Blood* 3 617
Shaffer J M Bluemle W Jun Sborov V and Neefe J R (1950) *Amer J Med Sci* 220 173
Sheldon J H (1935) *Haemochromatosis* London Oxford University Press
Sherlock S (1945) *Lancet* 2 397
— (1946a) *Ibid* 1 159
— (1946b) *J Path Bact* 58 523
— (1948) *Lancet* 1 817

Sherlock S (1951) *B it Heart J* 13 .73
— and Walshe V (1948) *Natu e Lond* 161 604
— — (1946) *Cl n Sci* 6 113
Shorr E (1947) *T ans 6th Conf Li er injury* p 33 Josiah Macy Jun Foundation New York.
Smyth H F and Smyth H F Jun (1936) *J Amer med Ass* 107 1683
Thannhauser S J (1940) *Lipoidoses* p 107 London Oxford University Press
Trowell H C (1949) *Trans R Soc t op Med Hyg* 4. 417
Uzman L and Denny Brown D (1948) *Amer J me l Sci* 215 599
Volwiler W Grindlay J H and Bollman J L (1950) *Gastroenterology* 14 40
Wade L Neudorff L Fritz H and Karl M (1948) *J Lab cl n Me l* 33 1123
Waterlow J C (1947) *Proc R Soc Med* 40 347
Watson C J and Hoffbauer F W (1946) *Ann intern Med* .5 195
— and Larson E A (1947) *Physiol Rev* 27 478
Whitman J F Rossmiller H R and Lewis L A (19 0) *J Lab cl n Med* 35 167
Wilson S A K (1912) *Brain* 34 .95
Witts L J (1947) *Brit med J* 1 45
Yannet H and Lieberman R (1946) *J Amer med Ass* 130 335

CHAPTER 32

PORTAL HYPERTENSION

R MILNES WALKER

DEFINITION

A RISE in the blood pressure in the portal circulation is always the result of some primary lesion and therefore cannot be considered as a disease on its own it is better to reserve the term portal hypertension for those instances where the whole of the portal bed takes part in this phenomenon and to exclude those relatively rare examples due to obstruction of one or other of the tributaries of the portal vein in which only a portion of the portal bed is affected from a practical point of view the only localized form results from obstruction of the splenic vein and for this the term splenic hypertension is more satisfactory

The normal pressure in the portal vein or its tributaries in man is from 80 to 140 millimetres of water when taking readings with a manometer no cardiac pulsation is seen but the changes in intra abdominal pressure which occur with respiration are transmitted to the portal blood In pathological states we have recorded pressures up to 560 millimetres of water

The pressure in a closed system depends partly on the pressure applied and partly on the peripheral resistance In the portal system the pressure applied comes from the splanchnic arteries by way of the capillaries in the alimentary canal spleen and pancreas or from the hepatic artery through its communication with the portal system in the liver parenchyma it is obvious that in health the former must be the greater pressure in order to maintain a flow of blood towards the liver but if the pressure in the liver rises sufficiently this flow may cease and blood in the portal vein come to a standstill clearly such a condition would be incompatible with life unless an adequate collateral circulation had developed between the portal venous system and the systemic veins The peripheral resistance depends on the resistance offered to the portal blood flowing through the portal vein or the liver parenchyma or to a rise in pressure in the inferior vena cava and hepatic veins in clinical states it is the resistance offered to the portal blood flow in the liver or portal vein which interests us for in cases where there is a rise in pressure in the inferior vena cava other effects overshadow the picture

The relative effect of the pressure transmitted by the circulation through the capillaries of the abdominal viscera other than the liver and through the hepatic artery has been studied by McMichael (1932) who found that in cats the normal portal pressure was 80–100 millimetres of water on clamping the mesenteric artery after ligature of the gastro duodenal artery the pressure fell to 50 millimetres of water and remained at that level if instead the hepatic artery was clamped a fall of 15–25 millimetres of water in the portal pressure occurred thus it appears

that in this animal the hepatic artery normally plays a part in maintaining the portal pressure We have been unable to show a similar effect in the human During the operation of cholecystectomy we have isolated the vessels running to the liver and observed the effects of their temporary occlusion on the pressure in a tributary of the portal vein Compression of the portal vein causes the pressure to rise rapidly to more than 500 millimeters of water but when the hepatic artery is obstructed no significant change occurs it appears therefore that in health the hepatic artery in man takes no part in maintaining the portal blood pressure but this requires further investigation Whether there are direct communications in the liver between the branches of the hepatic artery and the portal vein in man is still a matter of doubt Wakim and Mann (1942) claim that such channels are present in some animals and the experiments of Andrews Maegraith and Wenyon (1949) which we have confirmed support this contention

It has generally been assumed that in cases of chronic hepatitis it is the effect of fibrous tissue in the liver which is responsible for constriction of the blood vessels and the consequent increased resistance to the flow of blood The study of the amount and distribution of this fibrous tissue therefore assumes great importance The changes in the liver at the stage of the disease when the portal pressure is significantly raised consist of fibrosis often with round-celled infiltration and sometimes a remarkable increase in the number of bile ducts Some cases show fatty infiltration in the centre of the lobules and in one patient who had a pressure of 380 millimetres of water there was no fibrosis histologically but only such fatty infiltration it is of interest that this patient had had his first haematemesis 8 years previously In contrast to this we had another patient with a pressure of 365 millimetres of water with a history of 5 weeks only in whom areas of both fibrosis and necrosis were found

Microscopically the appearance of the liver varies greatly from case to case but three main types occur (1) the hob nail liver with coarse lobulation often paler than normal and usually about normal size but hard (2) a very fine lobulation and only slight increase in the firmness of its consistency and of normal colour in fact the gross changes may be overlooked if the examination is only casual but a biopsy will show fine fibrous trabeculae and (3) an enlarged plum coloured liver tense to the touch obviously congested and showing both fibrosis and areas of necrosis Histologically the most obvious change is some degree of fibrosis which is particularly marked along the portal tracts either narrow strands separating the lobules or coarser bands isolating whole groups of lobules in the latter case the amount of liver parenchyma may be much reduced and may represent little more than half the area of a section When there is a fine lobulation the strands of fibrous tissue may be very delicate but it is often such cases which have the higher portal pressures There is often some degree of infiltration by inflammatory cells particularly lymphocytes round the portal tracts and the great proliferation of bile ducts which is sometimes present has already been mentioned It has been impossible to demonstrate any simple relationship between the amount or distribution of fibrous tissue and the level of portal pressure and the actual cause of the rise in pressure requires further investigation

CAUSES OF PORTAL HYPERTENSION

Cases of portal hypertension may be divided into those with liver disease and those with obstruction to the portal vein or one of its major tributaries these have been described as intrahepatic or extrahepatic portal bed blocks but the term is a little misleading as in some of the extrahepatic cases the obstruction may involve the portal vein after it has entered the liver In the following classification localized cases of obstruction of the splenic vein are included

(1) Liver disease
   (a) Fibrosis following congenital atresia of the bile ducts
   (b) Chronic hepatitis
   (c) Haemochromatosis
   (d) Amyloid disease
(2) Portal vein obstruction
   (a) Congenital abnormalities
   (b) Thrombosis of the portal vein
   (c) Obstruction of the portal vein by pressure from without
(3) Localized obstruction (splenic hypertension)
   (a) Thrombosis of the splenic vein
   (b) Obstruction of the splenic vein by pressure from without

Liver disease

Fibrosis following congenital atresia of the bile ducts

It is surprising that all cases of this condition do not succumb during the early weeks of life but may recover from the initial obstructive jaundice and survive for a few years the intestinal mucosa taking on the function of excreting bile pigments such children develop a severe fibrosis of the liver and may present a few years later with an enlarged spleen and haematemesis or ascites In view of the severe liver damage it is not considered that surgery has any place in their treatment if it is not possible to restore the continuity of the biliary system during the first few weeks of life

We have seen two cases of this condition both of which were explored on account of persistent jaundice during the early weeks of life and no extrahepatic biliary passages could be found when seen at the age of 3 and 4 years respectively they had enlarged nodular livers moderately enlarged spleens and ascites One of them died at the age of 3 years 11 months of liver failure but no autopsy was obtained the other survived until the age of 5 years when he succumbed to a haematemesis and the autopsy confirmed the diagnosis of absence of bile ducts outside the liver Apart from peritoneoscopy no surgical operation was undertaken on either of these children

Chronic hepatitis

This is the cause of the great majority of cases of portal hypertension It is the general opinion that most patients with what was formerly described as Banti s disease have some degree of hepatitis but the work of McMichael (1934) and of Cameron and de Sarum (1939) shows that in some of them it is probable that simultaneous changes occur in both the liver and the spleen and that the

splenic enlargement cannot be accounted for entirely by the hypertension It is a fact however that in every one of a group of patients in whom symptoms started after the early years of life and who may be presumed not to be cases of congenital portal vein obstruction inflammatory changes in the liver have been found on histological examination though the liver may look and feel almost normal

The causes of chronic hepatitis have been fully described elsewhere It will suffice to say here that in the majority of cases it has not been possible to establish the cause of hepatitis though some have had treatment for syphilis and hence exposure to serum jaundice and others give a definite history of an attack of acute infective hepatitis but where such a history is obtainable it usually precedes the onset of symptoms due to the hypertension by 4 to 8 years The 38 patients in my series who come under this head may be divided into two groups according to whether irregularity of the liver surface was nodular (typical hob nail liver) or whether the surface was finely granular or even felt and looked normal On the whole those with the fine granular livers had the larger spleens and the higher portal pressures but there were exceptions to this and a patient with one of the highest portal pressures recorded (500 millimetres of water) has a very nodular liver though the spleen is only moderately enlarged In those cases with the fine granular livers haematemesis was the presenting symptom but in those with gross nodular livers 9 presented with haematemesis 12 with ascites and one with both symptoms Those with the fine granular livers showed in general little or no evidence of disturbed liver function while about half those with the nodular livers showed either a reversal of the albumin globulin ratio a high alkaline phosphatase or abnormal thymol turbidity tests The ages at which the first symptoms appeared range from 16 to 65 years but the ascitic group were all over 32 with the exception of 1 patient aged 19 years In only a few of these was there evidence that alcohol played a part in the development of the hepatitis The surgical procedures which have been undertaken on 34 patients in this group are set out in the table on page 754 There is one patient who is interesting because she came under our care before she had any symptoms due to this condition She was a woman aged 30 years and was sent because her doctor had found great enlargement of her spleen Extensive oesophageal varices were present and at operation her portal pressure was found to be 220 millimetres of water The liver looked and felt normal but histology showed marked lymphocytic infiltration with no fibrosis Liver function tests had been normal Another patient is interesting She had an illness associated with ascites in 1946 when aged 15 years and attacks of haematemesis commenced a year later Her spleen was much enlarged and she had oesophageal varices At operation the liver showed the usual fine granular surface and there was periportal fibrosis In addition however there was thrombosis of her splenic vein with the result that portal pressure in the mesenteric vein was 280 millimeteres of water while that in a vein in the hilum of the spleen was 380 millimetres of water Reviewing the results of the surgical procedures in these cases it seems that operation is unlikely to benefit greatly those patients whose only symptom is ascites but in those who have severe bleeding a fatal termination may be postponed either by forming a portal systemic anastomosis or by an operation to divert the flow of blood from the oesophageal varices

Haemochromatosis

This condition may give rise to portal hypertension as a result of the fibrosis in the liver One example was a man aged 53 years who had had pigmentation of his skin for 9 years and liver function tests showed marked changes though he had no glycosuria Biopsy of the liver showed *haemosiderin present in great* amount

Amyloid disease

This condition can cause portal hypertension as shown by one case where the diagnosis was confirmed by liver and spleen biopsies and the portal pressure was 280 millimetres of water

Portal vein obstruction

Congenital abnormalities and thrombosis of the portal vein

It is well to consider these together Haematemesis is the only symptom and it commences during the early years of life Apart from these bleedings the patients look and feel perfectly well The liver is not enlarged but marked splenomegaly is present Removal of the spleen has no effect on the course of the disease and death from haemorrhage usually takes place before the end of the second decade

At a laparotomy there may be no abnormality detectable in the portal vein or the vein may be replaced by a number of tortuous vascular channels which communicate with each other and lie in front as well as behind the common bile duct

The characteristic autopsy finding has been described as a cavernomatous transformation of the portal vein Only one instance has come to autopsy but here the portal vein which was represented by a few dilated channels in its extrahepatic part ended in a number of dilated spaces just inside the liver and appeared to have no outlets or connections with the hepatic circulation It appears thus that in the majority of cases with normal livers the lesion dates from the time of birth there are two possibilities it is either a true congenital abnormality or the result of the thrombosis of the portal vein at the time of birth this in turn may be either an extension of the normal obliteration of the ductus venosus or an inflammatory thrombo phlebitis as a result of infection from the umbilical vein The variations in the appearances outside the liver could be accounted for by the varying extent of the thrombosis down the portal vein Further observations are needed to settle this question but the fact remains that the prognosis is serious

A personal series of cases includes 8 patients in this group and in each one attacks of haematemesis were the only symptoms Bleeding started in the earliest case at the age of 3 years and in the eldest at 14 years the average age being 8 In no case was there any ascites and liver function tests were normal Four of these patients had undergone splenectomy before and in each instance there had been a recurrence of bleeding In those where the spleen was still present its enlargement was considerable being at least 3 fingers breadth below the costal margin Histology of the liver was available in 7 of these and showed no abnormality The portal pressures in 6 have varied from 260 up to 450 millimetres of water with an average of 380 millimetres of water The exact pathology has only been ascertained in one case as the others still survive This patient died at the age of 6 years as a result of haemorrhage splenectomy having been carried out at the

age of 4 years followed a year later by a side to side porto caval anastomosis At the time of death one year later this anastomosis was completely occluded by thrombus and the portal vein after it entered the liver provided a typical example of the condition known as cavernomatous transformation as already described

Obstruction of the portal vein by pressure from without

When the portal vein is obstructed by pressure from without the causative lesion usually overshadows the portal hypertension and generally the common bile duct is obstructed simultaneously Malignant tumours either primary or metastatic in lymph nodes are the most common cause

Localized obstruction (splenic hypertension)

Thrombosis of the splenic vein

A few cases are on record of thrombosis of this vessel and if the coronary vein enters the splenic vein distal to the site of the obstruction oesophageal varices will result which may cause haemorrhage Though rare it is important to bear this in mind for these cases are the only ones which will be cured by splenectomy alone and probably account for the few records of permanent cure of patients with Banti s syndrome following this operation In such cases if the liver appears normal a reading of the portal pressure in a tributary of the superior mesenteric vein will of course be normal and thus indicate the treatment required In our series no such case has been encountered but one patient with hepatitis had in addition thrombosis of the splenic vein and exceptionally large collateral vessels running from the hilum of the spleen through the omentum to adhesions to the left side of the abdominal wall

Obstruction of the splenic vein by pressure from without

Obstruction of the splenic vein by pressure or invasion by tumour may occur and I have seen two such examples of splenomegaly in patients with carcinoma of the stomach invading the splenic vein Here treatment is directed to the primary cause Whipple (1945) has described such a case where the obstruction was brought about by scarring following injury to the pancreas and in such a rare instance splenectomy will effect a cure

EFFECTS OF PORTAL HYPERTENSION

The effects of the increased pressure in the portal circulation are felt in all the organs which drain into it The first changes occur in the spleen and all cases show some enlargement of this organ the extent of the enlargement however appears to have no relation to the level of the pressure and is more likely to be related to the rate at which it develops the age of the patient at the time of onset and possibly other factors Cameron and de Sarum (1939) have shown that the spleen can be transplanted into the abdominal wall and its normal blood supply and drainage cut off completely yet when fibrosis of the liver is induced the spleen will enlarge thus demonstrating that a humoral factor also exists In that type which was formerly known as Banti s disease the spleen is often grossly enlarged 1 000 grams or more whereas the microscopic changes in

the liver are minimal, Banti considered that the primary condition was in the spleen and that the fibrosis of the liver followed later but our experience agrees with the views of McMichael (1934) that liver changes are always present Apart from cases commencing with symptoms early in life and which can be considered to be congenital in origin some significant changes have been present in the liver in every one of this series where there is gross fibrosis in the liver presenting the classical hob nail appearance the spleen is not as a rule so much enlarged The histological appearances in the spleen have been fully considered by McMichael (1934) they comprise siderotic nodules peri arterial haemorrhages and fibrosis

Of interest to the surgeon are the changes which take place in the splenic vessels in a few cases the artery is much enlarged and tortuous and may even present aneurismal dilatations the vein varies in its size but is roughly proportional to the size of the spleen and may be in extreme cases as much as 3 centimetres in diameter in a few however it remains quite small Where the hypertension is of long standing the splenic vein becomes varicose and loses its elastic tissue thus becoming friable and unsuitable for the purpose of a venous anastomosis In these circumstances spontaneous thrombosis may occur in the portal system either in the mesenteric vessels causing intestinal infarction or in the splenic vein adding a localized splenic hypertension to the general portal hypertension

All patients with portal hypertension develop a collateral circulation the sites of these vessels have long been recognized and occur where there is a natural anastomosis between the portal and systemic venous circulations in the region of the cardia and of the oesophagus in the anal canal in the retroperitoneal tissues particularly the lieno renal ligament and in the ligamentous attachments of the liver including the falciform ligament which in advanced cases produces the visible veins around the umbilicus known as the caput medusae

In some patients this collateral circulation is adequate to carry away all the portal blood for cases have been described in which the portal vein has been occluded by a long standing clot at the time of death and in some of the congenital cases the portal vein has been found to end blindly at its entrance to the liver

Varicose veins in the oesophagus and cardiac end of the stomach occur mainly *in the submucous layer* but in advanced cases numerous venous channels can also be seen in the subserous tissues and even in the mediastinum and lower intercostal spaces They give no evidence of their presence unless rupture occurs with haematemesis or more rarely melaena When very large they may give rise to a slight sensation of a lump in the throat but usually there is no disturbance of deglutition However it is this group which is the only one which is of real consequence to the patient for the majority of patients with portal hypertension ultimately succumb as a result of the bleeding from these veins In cases of cirrhosis of the liver Patek and others (1948) have shown that when once haematemesis occurs the risk of further bleeding is such that half the cases die from this cause within a year In congenital cases haematemesis starts during the first few years of life but some patients in this group may survive to the third decade before this proves fatal The main interest of the surgeon is the possibility of removing this danger It is difficult to explain why these varicose veins are so liable to rupture and when they do why bleeding is so severe *It may be due to the fact that the lumen of the*

oesophagus normally has a low pressure transmitted to it from the pleural cavities through its wall thus providing no support for the veins but it has also been suggested that peptic ulceration of the oesophageal mucosa may be a contributory factor No evidence of such ulceration has been found however in autopsy specimens but in such cases the perforation is usually over a particularly prominent vein and it is possible that the trauma of a bolus of food passing over the projecting vein may be an additional factor

In the anal canal the collateral veins appear as internal haemorrhoids Symptoms from this cause in portal hypertension are rare in the younger age group but in older patients these symptoms may be the first sign of the underlying cause All patients therefore who develop internal haemorrhoids in later life should be examined with this in mind for it is rarely advisable to treat the haemorrhoids without alleviating the portal hypertension Though bleeding from such haemorrhoids may be persistent it is rarely sufficient to be dangerous and is not a cause of death in this group of patients

The collateral veins which develop in the retroperitoneal tissues and in the attachments to the liver are wholly beneficial to the patient They are most prominent in the falciform ligament running to the anterior abdominal wall retroperitoneally they occur in the lieno renal ligament which often contains a great number of small vessels other channels develop between the veins of the pancreas and colon to the adrenal renal and lumbar veins Any pathological adhesions from the omentum and the viscera to the abdominal wall may be a site for the development of large collateral veins If any surgical treatment is contemplated the presence of these veins may be a serious embarrassment to the surgeon and may sometimes prevent surgical procedures being carried out

Effects on the alimentary canal

Portal hypertension by itself does not cause obvious changes in the alimentary canal itself except for a certain degree of venous congestion apart from the two sites already mentioned where the collateral circulation develops No gross disturbance of digestive processes can be demonstrated unless there is also a severe disturbance of liver function

Peritoneum

It has often been stated that portal hypertension causes ascites This however is not correct for in many patients in our series and particularly in those with the highest levels of portal pressure ascites is usually absent When ascites is present in cases of portal hypertension it is evidence of disturbed liver function and the majority of patients with ascites show biochemical evidence of this most commonly in a disturbance of the plasma proteins It is natural to assume that the increased filtration pressure will help in the formation of ascites but other factors must be present which include a change in the plasma proteins and probably an increased capillary permeability In our own series of cases where full studies have been made there are 5 in the congenital group with an average portal pressure of 390 millimetres of water in none of whom was there any ascites In cases of hepatitis in which haemorrhage was the most prominent symptom and ascites either slight or absent the average pressure in 15 cases was 340 millimetres of water

while in 6 cases in whom ascites was present and haemorrhage slight or absent the average pressure was only 225 millimetres of water

In patients who have had long standing portal hypertension with disturbance of liver function in addition to ascites there is oedema of the subserous tissues This gives rise to thickening of the walls of the intestines which assume a grey colour and there is also thickening of the retroperitoneal tissues which makes dissection of individual structures difficult for the normal planes of cleavage—for example round large vessels—tend to disappear

SYMPTOMS AND CLINICAL FEATURES

Patients who have portal hypertension present with the symptoms of either haematemesis or ascites It is only in the minority that both symptoms occur in the same patient and then usually at different periods of time The pathology of these two symptoms has already been discussed In addition there may be clinical evidence of disturbed liver function such as the characteristic brown complexion digestive disturbances lethargy spider naevi or palmar erythema On physical examination unless the abdominal distension prevents it the spleen is usually palpable and may be enlarged to 4–5 finger breadths below the costal margin The liver may also be palpable but it varies within wide limits both in size and consistency Sometimes the dilated veins of the abdominal wall are visible and the flow of blood above the umbilicus is in an upward direction

DIAGNOSIS

The diagnosis of portal hypertension is as a rule not difficult The demonstration of oesophageal varices is proof that the case is one of portal hypertension or its localized form splenic hypertension and in the absence of an obvious cause of obstruction of the splenic vein or evidence of liver disease the distinction between these two cannot be made except at a laparotomy The presence of these varices is shown by examination of the oesophagus with a barium swallow when they appear as rounded filling defects most marked at the lower end but in severe cases extending even as high up as the cervical portion of the oesophagus In the less advanced cases however there may be difficulty in demonstrating these and if doubt still exists the oesophagus should be examined with the oesophagoscope when the veins will show as blue rounded projections under the epithelium or in more advanced cases where they are large and surround the lumen they have an appearance very similar to internal haemorrhoids Great care is needed during this examination not to damage them in view of their liability to rupture Other investigations to exclude alternative causes of splenomegaly may be necessary Infra red photography of the abdominal wall may be helpful in showing dilated subcutaneous veins which are not visible with ordinary light When the diagnosis has been made it is important to obtain as clear an idea as possible of the functional state of the liver It has already been noted that ascites, if present is an indication of some liver damage but help may also be obtained from biochemical investigations For these purposes an estimation of the plasma proteins is the most helpful for where liver damage is severe there is nearly always a fall in the albumin level where this is lower than the globulin level liver damage is always considerable

Readings below 3 5 grams per 100 millilitres usually indicate some pathological damage in the liver while if the albumin level is below 2 5 grams per 100 millilitres the prognosis is serious and below 2 grams per 100 millilitres the risk of surgical intervention is great This figure is far from static and by means of medical treatment it may show considerable improvement It must also be taken into account that where repeated tappings of ascitic fluid have been made the loss of protein from this cause may depress the serum protein levels Few patients have shown an abnormally high alkaline phosphatase level but it is interesting that abnormalities in this direction have been found when the plasma proteins have been normal and it indicates a severe degree of liver damage The thymol turbidity thymol flocculation and colloidal gold tests have given little help and have only been grossly abnormal in one patient who in fact had a liver which showed very little change histologically The serum bilirubin level has also been almost invariably within normal limits and no patients have shown frank jaundice The presence of severe jaundice seems to be a terminal event Peritoneoscopy has a place in the investigation of these cases particularly those with ascites the surface and consistence of the liver can be studied venous collaterals will be observed in the falciform ligament and biopsy specimens can be taken from a selected part of the liver It is considered that this procedure is safer and gives more reliable information than aspiration liver biopsy which has certain drawbacks in cirrhotic patients (Sherlock 1950)

METHODS OF TREATMENT

As portal hypertension is a secondary condition the treatment of it may be described as always palliative except in those congenital cases in which there is an obstruction to the portal vein where the production of a by pass may be considered curative If there is evidence of associated chronic hepatitis this must receive the appropriate medical treatment

Surgical treatment aims at preventing death from haemorrhage It has also been employed in the past in an attempt to relieve persistent ascites but it is doubtful whether the operations which have been carried out have played much if any part in the relief which has been reported

The methods employed are as follows

(1) Those which aim at reducing the portal pressure
- (a) by reducing the blood entering the portal circulation
  - (i) splenectomy
  - (ii) splenic artery ligation
- (b) by promoting collateral circulation
  - (i) by promoting vascular adhesions
  - (ii) by a direct venous anastomosis

(2) Those which divert the blood away from the oesophageal varice
- (a) a direct attack on the varices
  - (i) injection and thrombosis of the varices
  - (ii) excision of the varices
  - (iii) multiple ligation of the varices
- (b) division of vessels leading to the varices
- (c) promoting collateral circulation around the varices

Methods which aim at reducing the portal pressure

Reducing the blood entering the portal circulation

Splenectomy —Howells (1938) made a study of 94 patients who were suffering from Banti s syndrome amongst whom 57 splenectomies were carried out and he came to the conclusion that there was no significant difference in the survival rates when compared with those who were treated by non operative means Experience of patients on whom splenectomy has been carried out leads to the same conclusion In every case of splenectomy where haemorrhage was the presenting symptom further bleeding has occurred one patient having slight haemorrhage

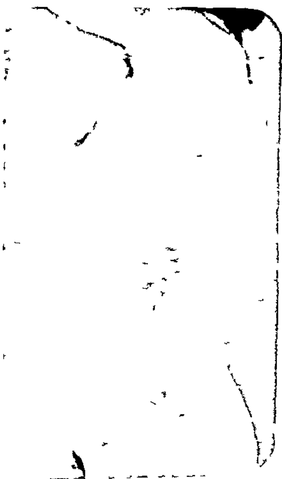


FIG 263 —Caput medusae in relation to scar 3 years after splenectomy (infra red photograph)

10 years after the splenectomy and more severe haemorrhage 3 years later In the patients re operated on following splenectomy there have been extensive vascular adhesions between the omentum and the abdominal wall of the splenic bed and I am inclined to think that the benefit which results from the operation is due at least in part to this collateral circulation which has developed In one patient—who also had a lieno renal anastomosis which probably became occluded—

extensive veins could be seen in the subcutaneous tissue overlying the bed of the spleen Many patients with portal hypertension develop quite a considerable collateral circulation in the attachments of the spleen particularly in the lieno renal ligament and it is considered that these vascular channels should be preserved and therefore splenectomy by itself is definitely contra indicated

Splenic artery ligation—This operation which was first suggested by McNee (1931) seems to have been first undertaken deliberately by Watson (1935) It is said that removal of the spleen cuts down the amount of blood entering the portal circulation by from 25 to 40 per cent and though ligature of the artery alone may not have quite such an effect it will materially reduce the portal pressure Results of this operation have however been disappointing for in 2 out of 9 there has been a recurrence of the bleeding but it is a simple procedure and it is regarded as a useful adjunct to other methods in fact it is a general routine procedure whenever a laparotomy is performed in these cases The artery can be exposed through the lesser sac as it runs along the upper border of the pancreas and it is preferred to ligature it as near to the spleen as possible There seems to be no serious risk of splenic necrosis In some cases the spleen shows a definite reduction in size but in others there appears to be no change

Promoting collateral circulation

Promoting vascular adhesions—Many methods have been adopted for this purpose The Talma Morrison operation was introduced independently by these two surgeons Its aim is to promote adhesions between the liver and spleen and parietal peritoneum and also between the greater omentum and the anterior abdominal wall In the past it has been employed in the cases of alcoholic cirrhosis with a view to the relief of ascites and it may have its uses when all other methods of treatment are impracticable but its value in diminishing the risk of haemorrhage is not proved

Direct venous anastomosis—Although a number of attempts have been made in the past to form a venous anastomosis between the portal and systemic circulations its introduction on a larger scale derived from the work of Whipple (1945) was undertaken by Blakemore and Lord (1945) The latter authors devised an ingenious method with a vitallium tube avoiding the use of sutures in the vein walls but which brought the intima of the two veins into contact without any raw surface Improvements in the technique of vascular anastomosis have however superseded this method and an eversion suture technique is generally used for the purpose The first successful operations were carried out after removal of the spleen and left kidney and end to end anastomosis of their respective veins or by division of the portal vein and implantation of its end into the inferior vena cava Since then the main modification in technique which has been generally accepted has been the preservation of the left kidney and the junction between the end of the splenic vein and the side of the renal vein Many such operations have now been recorded but it is difficult to assess the results without a very long follow up It is however true that the early enthusiasm is beginning to wane and the long term results have not been as satisfactory as was at first hoped

Methods which aim at reducing the portal pressure

Reducing the blood entering the portal circulation

Splenectomy.—Howells (1938) made a study of 94 patients who were suffering from Banti's syndrome amongst whom 57 splenectomies were carried out and he came to the conclusion that there was no significant difference in the survival rates when compared with those who were treated by non operative means. Experience of patients on whom splenectomy has been carried out leads to the same conclusion. In every case of splenectomy where haemorrhage was the presenting symptom further bleeding has occurred, one patient having slight haemorrhage

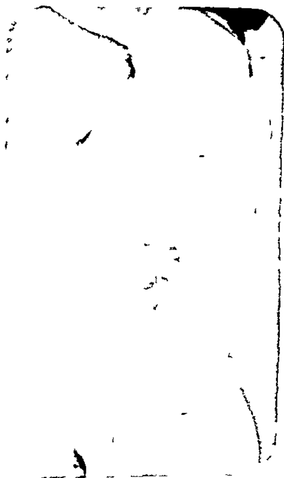


FIG. 763.—Caput medusae in relation to scar 3 years after splenectomy (infra red photograph)

10 years after the splenectomy and more severe haemorrhage 3 years later. In the patients re operated on following splenectomy there have been extensive vascular adhesions between the omentum and the abdominal wall of the splenic bed and I am inclined to think that the benefit which results from the operation is due at least in part to this collateral circulation which has developed. In one patient—who also had a lieno renal anastomosis which probably became occluded—

vascular channels leading into the mediastinum Gray and Whitesell (1950) have also carried out devascularization of the lower part of the oesophagus and the cardia and combined this with vagotomy in order to reduce the gastric acidity which they consider may be responsible for causing erosions of the vessels In order to avoid the gastric distension consequent upon a vagotomy they also recommend a gastro enterostomy

Multiple ligation of the varices—Boerema (1949) has advocated opening the oesophagus and putting multiple ligatures round the varicose veins and injecting a sclerosing solution into the veins between the sutures and has reported two patients in which this has been done Crile (1950) recommends a similar method using continuous cat gut stitches and no sclerosing solution When no intra abdominal procedure has been feasible some cases have been treated by exposing the oesophagus through the left pleural cavity dividing it just above the cardia and re suturing it after under running the larger varices with cat gut sutures It is too early yet to assess the results but post operative radiological examination indicates a marked reduction in the size of the varices

Division of vessels leading to the varices

The aim of this operation is to divert the blood from the dangerous oesophageal veins into other channels by cutting their supply from the portal circulation This supply is mainly through the left gastric vein the vasa brevia and veins in the wall of the stomach The procedure described by Tanner (1950) as portal azygos disconnection consists in division of the above mentioned veins and transection of the stomach high up which is then re sutured The left gastric artery is retained in order to preserve the blood supply to the fundus of the stomach It is still too early to assess the results of this operation which can only be considered palliative but it has been used on four occasions in all cases of which there had been a relapse following a splenectomy or ligature of the splenic artery

Promoting collateral circulation around the varices

This has been advocated by Garlock and Som (1950) who have attempted to encourage the formation of vascular channels between the oesophagus and the mediastinum by packing the posterior mediastinum with gauze for 12–14 days This had been carried out on 8 patients and good results are claimed with 3 of these

Of 47 operations on 42 patients with portal hypertension 18 have been venous anastomoses with 3 deaths during the early part of the series 2 patients died as a result of leakage from the anastomosis and the third succumbed as a result of mesenteric thrombosis one month after operation With the exception of the patient already referred to who had a cavernomatous transformation of the portal vein and died a year after a porto caval anastomosis the remaining 14 were still alive for periods up to 4 years but in 3 patients the operation was done for ascites and 2 of these have obtained little relief Of the remainder 3 still have severe varices and it is probable that their anastomoses have become occluded In 1 of these a gastric transection operation has already been undertaken and another is awaiting a similar operation The 8 patients who have had either the gastric or

Blakemore and Lord (1949) reported the results of 62 cases of venous shunt In 18 in which the liver was normal and the obstruction was recorded as extra hepatic there were 2 operative deaths 2 patients succumbed to further haemorrhage 5 had further haemorrhage and 9 were reported symptom free As regards the intrahepatic cases there were 8 operative deaths 11 have subsequently died 4 are alive with recurrence of symptoms and 21 have remained well Of these cases 45 had had spleno renal anastomoses in 10 the portal vein was anastomosed to the inferior vena cava or right renal vein and other veins were used in 7 In a further report (Blakemore 1950) bringing the total number of cases up to 79 there have been 16 deaths during the post operative period and 12 subsequent deaths 6 of which were due to further haemorrhage Amongst those who have died the majority showed occlusion of the anastomosis In my own cases 18 venous anastomoses of one type or another have been performed with 3 deaths in the post operative period and one subsequent death In this case a side to side porto caval anastomosis the opening was completely occluded when death took place 1 year afterwards Four cases have been treated by ligature of the splenic artery and side to side anastomosis between the splenic vein and left renal vein This has the advantage that it preserves any natural collateral circulation which has already developed around the spleen for the latter organ may in these cases be adherent by many vascular bands thus making this part of the operation difficult and sometimes risky to the patient Any surgeon who explores these patients with portal hypertension should be prepared to carry out a venous anastomosis if it seems indicated The conclusion has been reached however that unless the blood vessels are very large and an opening of at least 1 5 centimetres in diameter can be made it is not worth while attempting a venous anastomosis In very few patients has there been easy access to the portal vein or has the vein itself been suitable for an anastomosis In some the vein is replaced by a number of varicose channels while in others it is surrounded by vascular connective tissue which prevents dissection and isolation of an adequate length of the vein

Methods which divert the blood away from the oesophageal varices

A direct attack on the varices

Injection of the veins with a sclerosing solution through the oesophagoscope — This method was introduced by Crafoord and Frencker in 1939 but the amount of thrombosis which can be caused by a single injection is small and when one observes the extent of the varices in these patients it is unlikely that this method will have anything but a very temporary effect and it is rarely employed nowadays

Excision of the varices —This was advocated by Phemister and Humphreys (1947) who reported two patients In one case the lower part of the oesophagus and the adjacent part of the stomach was resected and in the other the whole stomach The latter patient had had two further haemorrhages within two years of his operation and it seems that less severe measures may have an equally good effect Allison (1950) has carried out extensive excisions of the submucous veins through a left thoracotomy dividing every possible vessel passing in and out of the oesophagus from the level of the left main bronchus to the cardia carefully preserving the

in the oesophagus should be made by the passage of a tube with a rubber balloon attached resembling a Miller Abbott tube so that the balloon occupies the lower third of the oesophagus and is inflated to a pressure sufficient to occlude the veins The tube is retained in place for 3–4 days and fluids can be administered into the stomach through it The value of this method is not yet definitely proved but it should certainly be attempted when bleeding is serious (Rowntree and others 1947)

MANAGEMENT OF PORTAL HYPERTENSION

When a diagnosis has been made the management of the case must be decided upon and this depends upon the symptoms and the functional state of the liver

As regards the latter the general condition of the patient should be particularly considered lethargy poor appetite and a brown complexion or frank jaundice are signs of poor liver function and if these are accompanied by a serum albumin below 3 grams per 100 millilitres or a reversal of the albumin globulin ratio if the alkaline phosphatase is above 15 or the flocculation tests show gross abnormality operation should be undertaken with caution and probably only a limited procedure carried out

When there has been severe bleeding and liver function is not impaired it is believed that a laparotomy should be performed for this a mid line incision above the umbilicus will serve but if the surgeon has a porto-caval shunt in mind a right thoraco-abdominal incision through the bed of the ninth or tenth rib gives much the best access and all the necessary exploration except a splenic biopsy can be carried out through this incision The liver and spleen are first examined and if desired portions removed for biopsy purposes it is wise next to measure the portal pressure and after some experience it is most satisfactory to do this through one of the veins in the omentum or the mesentery of the jejunum the selected vein is isolated and fine ligatures are placed round it the distal one being tied a plythene cannula connected to a manometer con taining citrate solution and reading up to 500 millimetres is then introduced through a nick in the vein and the second ligature tightened by a half knot around it It is important to see that there is no pull on the mesentery or pressure by retractors on the portal vein but if the cannula is properly placed there will be a rise or fall in the manometer as it is lowered or raised and small excursions coincident with respiration will be seen The manometer is held with the zero reading on a level with the portal vein as the measurement is taken On removing the cannula the second ligature is tightened and the knot completed If the pressure is found to be normal the case may be one of splenic hypertension The splenic vein should then be exposed and examined and if no obvious cause of obstruction in this vein is found the pressure inside it near the spleen should be measured If it is such a case the liver being normal splenectomy should be carried out

Having ascertained that the portal pressure is raised a decision on the best treatment must be made The surgeon will have in mind the performance of a portal systemic venous shunt but unless a wide communication can be made this

oesophageal transection are all too recent to give any conclusive results but one had a recurrence of haemorrhage 6 months after and has since had a porto caval anastomosis

TABLE I

CASES OF CHRONIC HEPATITIS *

39 Operations on 35 Patients

Operation	No of cases	Operative deaths	Recurrence of symptoms	Later deaths	Symptom free	
					Number	Average period (months)
Splenectomy only	6	2	2	2		
Splenectomy and end to-side spleno-renal anastomosis	7	3	3		1	30
Ligature of splenic artery	11	1	1	1	8	13
Ligature of splenic artery and side to-side spleno-renal anastomosis	2		1		1	5
†Porto-caval anastomosis	3				3	17
Portal systemic anastomosis using other vessels	1				1	30
Division left gastric vein (previous splenectomy)	1				1	17
‡Gastric or oesophageal transection	6		1		5	3
Omentopexy	2		2			
CASES OF CONGENITAL PORTAL VEIN OBSTRUCTION						
No operation (previous splenectomy)	1					
Division of splenic artery and side to side spleno-renal anastomosis	2		1		1	12
Portal systemic venous anastomosis (previous splenectomy)	2			1	1	36
Splenectomy and spleno renal anastomosis	1		1			
Division of splenic artery followed later by gastric transection	1				1	7
Gastric transection (previous splenectomy)	1					

* Including one case of haemochromatosis
† One had previous gastric transection
‡ Two had previous splenectomy and spleno-renal anastomosis and one had previous splenic artery ligature and spleno-renal anastomosis

Since these figures were collected four more cases have had porto-caval anastomoses three by end to-side and one by the insertion of a vein graft None of these patients has had further haemorrhage up to date

TREATMENT OF HAEMATEMESIS DUE TO PORTAL HYPERTENSION

In view of the serious danger to life from bleeding from the oesophagus or upper end of the stomach measures may be required in an emergency to control it Apart from giving blood transfusions an attempt to compress the distended veins

the view is expressed here that these operations which are by no means free from risk should not be performed unless large vessels are available and a wide opening can be made In contrast to this the more recent trend is towards means of diverting blood from the dangerous oesophageal varices or else a direct attack on these varices

REFERENCES

Allison P R (1950) *Ann Surg* 132 808
Andrews W H H Maegraith B G and Wenyon C E M (1949) *Ann t op Med Parasit* 43 229
Blakemore A H (1950) Personal communication
— and Lord J W (1945) *Ann Surg* 122 476
— — (1949) *Advances in Surgery* 1 337
Boerema I (1949) *Acta Chir Neerland* 1 253
Cameron G R and de Sarum G S W (1939) *J Path Bact* 48 41
Crafoord C and Frencker P (1939) *Acta Otolaryng* 27 4?
Crile G (1950) *Arch Surg* 61 654
Garlock J H and Som M L (1950) *J thorac Surg* 19 57_
Gray H K and Whitesell F B (1950) *Ann Surg* 132 798
Howels L (1938) *Lancet* 1 1370
Linton R R and others (1948) *Surg Gynec Obstet* 87 179
McMichael J (193) *J Physiol* 75 241
— (1934) *J Path Bact* 39 481
McNee J W (1931) *Lancet* 1 1069
Patek A J and others (1948) *J Amer med Ass* 138 543
Phemister D B and Humphreys E M (1947) *Ann Surg* 126 397
Rowntree L G and others (1947) *J Amer med Ass* 185 630
Sherlock S (1950) *Postgrad Med J* 24 472
Tanner N C (1950) *Proc R Soc Med* 43 147
Wakim K G and Mann F C (1947) *Anat Rec* 82 233
Watson R B (1935) *Brit Med J* 1 821
Whipple A O 1945) *Ann Surg* 122 449

should not be attempted I have no doubt personally that in *some cases when* carrying out this procedure I have removed more collateral vessels which nature has provided than I have produced by the shunt so unless large veins are available *for this purpose some other procedure is better*

Blakemore considers that an anastomosis between the portal vein and inferior vena cava is the most effective and gives the best results It is early to form an opinion about this but recent experience with end to side porto caval anastomosis after division of the portal vein shows that it is technically not so difficult as a side to side anastomosis and gives a *wide opening carrying a greater stream of* blood so that it seems much less likely to become occluded subsequently In making such an anastomosis a right thoraco abdominal incision is the only method of exposure which has proved really adequate The disadvantage of this incision is that if the portal vein is found unsuitable no alternative procedure can be undertaken without a fresh incision

The surgeon will therefore inspect the portal vein and the splenic vein in congenital cases the portal vein is unlikely to be suitable for an anastomosis in *acquired cases this vein may have undergone some degree of thrombosis or* may be surrounded by very vascular connective tissue which oozes freely and renders adequate exposure of the portal vein impossible

If the splenic vein is large it may be used for an anastomosis to the left renal vein after mobilization of the tail of the pancreas This is not the place to describe the technical details but in such cases the splenic artery should be ligatured and divided and a side to side anastomosis should be made between the splenic and left renal veins using an everting suture of silk which brings intima in contact with intima

CONCLUSION

It will be realized that the large number of surgical methods which have been employed tow*ards the relief of portal hypertension is an indication that not one* of them is entirely satisfactory or can be applied to all cases it is only in the last 5 years that renewed awakening of interest in this condition has been widespread and this is far too short a time to evaluate long term results in a condition which is so capricious The surgeon who elects to treat these cases must be aware of the possibilities which are available and must also be on the alert to change his tactics even during an operation he must be experienced in vascular suturing and equally at home working in the thorax or the abdomen and if he is to assess his patients *adequately he must be conversant* with the use of the oesophagoscope

No evidence can be found that splenectomy is of benefit in cases of generalized portal hypertension and the performance of this operation may prevent an adequate vascular shunt being car*ried out at a later date a plea previously* ex pressed by Linton (1948) and reiterated by others is therefore again put forward that this operation should be abandoned unless the surgeon is prepared to carry out a vascular anastomosis at the same time

On the basis of statistics available at present it is quite impossible to come to *definite* conclusions regarding the long term results of any particular method Owing to the great tendency for venous shunts to become occluded by thrombosis

bile-duct the pancreas becomes the seat of an obstructive lesion of the Banting type The ducts dilate and the glandular tissue slowly atrophies with some increase in the fibrous stroma This is of great importance to the surgeon for the pancreas which is the seat of an obstructive lesion of this kind feels hard and nodular to the touch Some difficulty may be found in distinguishing the border line between malignant tissue and obstructive gland Even more puzzling is the case in which the causative tumour is so small that it cannot be palpated for the gland may then be assumed to be the seat merely of chronic obstructive pancreatitis It has been increasingly impressed upon us that if pancreatic calculus a very rare lesion can be excluded chronic obstructive pancreatitis is always due to neoplastic occlusion of the pancreatic duct

The pathological effect on the liver is equally important The biliary passages dilate and a hydrohepatosis develops The liver is swollen and its sharp edge becomes rounded and there may be visible dilated bile channels on its surface The mechanism whereby carcinoma of the pancreas effects an occlusion of the common bile duct is still obscure In most cases a probe can be passed without difficulty along the dilated common bile duct passing the region of the tumour into the duodenum The suggestion that the carcinoma may in some way produce a reflex spasm of the sphincter of Oddi does not appeal to one s common sense Carcinomas in the neighbourhood of other sphincters do not commonly have this spastic effect

Obstruction of stomach or duodenum by the pancreatic tumour or obstruction of the mesenteric or portal vein with the development of ascites and intestinal congestion no less than invasion of the vena cava with production of oedema of the lower extremities is of little interest to the surgeon for by the time these effects become manifest the pancreatic tumour may confidently be regarded as irremovable

The spread of tumours of the ampullary region and of the pancreas is relatively local in its scope Direct spread occurs early from pancreas to bile passages or from bile passages into the substance of the gland Later the duodenum may be invaded or the portal vein or mesenteric vein or even the inferior vena cava In late cases of carcinoma of the body of the pancreas the tumour may invade the stomach to ulcerate into it and to produce a malignant mass in the upper abdomen the primary site of which can sometimes not be discerned

The lymphatic spread of tumours in the region of the head of the pancreas is also local until a late stage The glands primarily invaded are those lying on the posterior surface of the head of the organ or in the sulcus between the head of the pancreas and the duodenum These lymph nodes and the subpyloric node are removed with all modern forms of pancreatico-duodenectomy The lymph drainage from the lower part of the head and from the uncinate process is though quite local sometimes more dangerous in its effect These areas may drain directly to lymph nodes in the root of the mesentery and a quite early tumour in this situation may be inoperable by reason of enlarged malignant glands around the termination of the superior mesenteric vein Further spread by lymph pathways is commonly by way of the common duct and it is not unusual to find a chain of glands along the common duct and extending even upwards into the hilum of the liver

CHAPTER 33

CARCINOMA OF THE PANCREAS

IAN AIRD

THE INTRODUCTION of vitamin K 10 or 12 years ago opened new fields to the surgeon interested in malignant disease of the pancreas and of the biliary tract Since its introduction there has been no hazard of capillary bleeding at operation and full exploration of the pancreas with removal of considerable parts of it or even of the whole gland has become technically possible Whether improvements in operative surgery have increased the average duration of life in the patient who suffers from carcinoma of the pancreas is open to doubt I have no patient surviving for a period of longer than a little over 2 years and yet before the introduction of pancreatectomy as a practicable procedure there were several patients under my care who survived for 3–4 or in one case 6 years after the performance of a palliative operation for carcinoma of the head of the gland Even during the period of survival the patient who has undergone pancreatectomy is not always comfortable and happy There is some reason to believe that the line of anastomosis between the pancreatic duct and the intestine may sometimes become occluded in convalescence and give rise to a form of pancreatic diarrhoea which has a high nuisance value and symptoms occur too which are suggestive of ascending infection of the biliary tract The relative ease however with which carcinoma of the ampulla of Vater or of the termination of the common bile duct can be eradicated makes disease of this region more attractive than carcinoma of the pancreas proper and it is the surgery of these ducts which seems to offer most hope in the immediate future

PATHOLOGY

Carcinoma in the region of the pancreas whether it arises from the pancreas itself or from the termination of the common bile duct has its origin in columnar epithelium It may present either as a proliferative tumour as a spreading infiltration throughout the affected tissue or as a malignant ulcer eroding into the duodenum Histologically it may show either a well marked glandular structure or a spheroidal celled or scirrhous architecture

The relatively early view which operation now gives to carcinoma of the pancreas demonstrates fairly clearly that if the very rare carcinoma of the islets be excluded carcinoma of the pancreas takes its origin from the main pancreatic duct or one of its larger tributaries

At a time when carcinoma of the pancreas or ampulla or bile duct is amenable to surgery it exercises pathological effects on the pancreas and on the liver If the pancreatic duct itself is occluded as it is by all carcinomas of the duct of Wirsung and by many carcinomas of the ampulla and termination of the common

bile-duct the pancreas becomes the seat of an obstructive lesion of the Banting type. The ducts dilate and the glandular tissue slowly atrophies with some increase in the fibrous stroma. This is of great importance to the surgeon, for the pancreas which is the seat of an obstructive lesion of this kind feels hard and nodular to the touch. Some difficulty may be found in distinguishing the border line between malignant tissue and obstructive gland. Even more puzzling is the case in which the causative tumour is so small that it cannot be palpated, for the gland may then be assumed to be the seat merely of chronic obstructive pancreatitis. It has been increasingly impressed upon us that if pancreatic calculus, a very rare lesion, can be excluded, chronic obstructive pancreatitis is always due to neoplastic occlusion of the pancreatic duct.

The pathological effect on the liver is equally important. The biliary passages dilate and a hydrohepatosis develops. The liver is swollen and its sharp edge becomes rounded and there may be visible dilated bile channels on its surface. The mechanism whereby carcinoma of the pancreas effects an occlusion of the common bile-duct is still obscure. In most cases a probe can be passed without difficulty along the dilated common bile-duct, passing the region of the tumour, into the duodenum. The suggestion that the carcinoma may in some way produce a reflex spasm of the sphincter of Oddi does not appeal to one's common sense. Carcinomas in the neighbourhood of other sphincters do not commonly have this spastic effect.

Obstruction of stomach or duodenum by the pancreatic tumour, or obstruction of the mesenteric or portal vein with the development of ascites and intestinal congestion, no less than invasion of the vena cava with production of oedema of the lower extremities, is of little interest to the surgeon, for by the time these effects become manifest the pancreatic tumour may confidently be regarded as irremovable.

The spread of tumours of the ampullary region and of the pancreas is relatively local in its scope. Direct spread occurs early from pancreas to bile passages, or from bile passages into the substance of the gland. Later the duodenum may be invaded, or the portal vein or mesenteric vein, or even the inferior vena cava. In late cases of carcinoma of the body of the pancreas the tumour may invade the stomach to ulcerate into it and to produce a malignant mass in the upper abdomen, the primary site of which can sometimes not be discerned.

The lymphatic spread of tumours in the region of the head of the pancreas is also local until a late stage. The glands primarily invaded are those lying on the posterior surface of the head of the organ, or in the sulcus between the head of the pancreas and the duodenum. These lymph nodes and the subpyloric node are removed with all modern forms of pancreatico-duodenectomy. The lymph drainage from the lower part of the head and from the uncinate process is, though quite local, sometimes more dangerous in its effect. These areas may drain directly to lymph nodes in the root of the mesentery, and a quite early tumour in this situation may be inoperable by reason of enlarged malignant glands around the termination of the superior mesenteric vein. Further spread by lymph pathways is commonly by way of the common duct, and it is not unusual to find a chain of glands along the common duct and extending even upwards into the hilum of the liver.

Blood spread to the liver is quite late in tumours of the head of the pancreas and the region of the ampulla though liver metastases are not infrequently present at death in tumours of the body of the gland

CLINICAL FEATURES

The patient suffering from pancreatitis may present in one of several different ways Most commonly the primary complaint is of obstructive jaundice but on occasion the first symptom may be of abdominal pain (especially in tumours of the tail and body of the gland) diarrhoea of a pancreatic type or merely a progressive aesthenia That patient is most fortunate who presents first with jaundice for in him the diagnosis is not likely to be long delayed

Happy were the days when Courvoisier s law was regarded as immutable and when carcinoma of the pancreas or ampulla or of the common bile duct was held to produce classically and constantly a progressive painless deepening jaundice with an enlarged palpable gall bladder The more one sees of pancreatic cancer the more suspicious one becomes of so classical a clinical picture I have already mentioned that jaundice may in the first instance be absent and one patient complained of persistent and unexplained abdominal pain for a period of 2 years before a diagnosis was made Abdominal pain unaccompanied by jaundice particularly if it is of pancreatic type relieved by a crouching position should raise the suspicion of pancreatic disease if no other abdominal lesion can be found to explain it It is surprising how severe this pain sometimes is

Even when jaundice is present it is by no means always progressive and it is indeed surprising how often there are one or more intermissions jaundice clearing for 1 or 2 days or even 1 or 2 weeks in some cases Why jaundice due to carcinoma of the ampulla for example should be so remarkably intermittent in some cases is quite obscure but probably the waxing and waning of local oedema can explain some intermissions while others may be due to a tumour of the ampulla bursting into the duodenum with the establishment of a malignant fistula between duct and duodenum a fistula which is later closed by further growth of the tumour Why tumours of the pancreatic duct may sometimes produce intermittent jaundice is as obscure as the mechanism by which they produce jaundice at all at early stages of their growth

A palpable gall bladder in the presence of obstructive jaundice is perhaps still the best evidence of the presence of a neoplasm in the region of the termination of the common bile duct but even this sign is not entirely constant The gall bladder may be enlarged though rather rarely in case of a calculous obstruction if the common duct is acutely occluded by a sterile stone such as the pigment stone in haemolytic anaemia The commonest exception to the rule of the enlarged gall bladder however is the patient with malignant disease whose gall bladder is quite small In most cases of this clinical anomaly the primary pancreatic tumour has spread to glands of the common duct above the level of the junction of cystic and hepatic ducts and the real obstructing lesion is not the primary tumour but the secondary just at the hilum of the liver

Special methods of investigation afford a good deal of help not only in making the diagnosis of carcinoma of the pancreas but also in showing the patient s suitability for operation

The gastric acidity is not of much value The majority of my patients who suffer from carcinoma of the ampullary region are nearly or completely achlorhydric No explanation has yet been advanced for this and it is not known whether carcinoma of the pancreas is commoner in congenital achlorhydria as carcinoma of the stomach is or whether once the carcinoma develops it produces a secondary achlorhydria by some mechanism not yet understood It is always valuable to test the stool for occult blood The presence of occult blood is highly suggestive of an ampullary lesion though like most data concerning cancer of the pancreas the rule is not a universal one Nearly 10 per cent of patients who have suffered from carcinoma of the head of the pancreas or of the region of the ampulla have suffered coincidentally from peptic ulceration of the first part of the duodenum and it is not always clear which of these lesions is responsible for bleeding

A bismuth series may offer information of some value Distortion of the duodenum is seldom obvious at a time when surgical intervention is likely to be considered but widening of the curve of the duodenum is highly suggestive of carcinoma of the head of the pancreas and a tumour of the region of the ampulla may even give a filling defect resembling either a figure 3 or a reverse figure 3 of the medial wall of the second part of the duodenum Duodenal obstruction measurable radiologically is never present until the very latest stages of the disease

It is customary to employ a battery of chemical tests in the assessment of a case of carcinoma of the pancreas A positive Van den Bergh reaction is usual as in all cases of obstructive jaundice though in later stages of the disease this may be equivocal The actual degree of jaundice as measured clinically and by estima tion of the serum bilirubin is usually relatively high and steadily progressive if investigated over a long period though as we have seen an increase of serum pigment may not be steadily progressive Urobilinogen is absent from the stool and from the urine as in all forms of obstructive jaundice Serum phosphatase is higher usually in this disease than in any obstructive biliary lesion The plasma protein is reduced and the albumin globulin ratio disturbed only in cases after quite prolonged biliary obstruction with advancing liver failure and these are a good measure of the way in which the patient will tolerate operative intervention The thymol turbidity and other flocculation tests if positive are also a sign of threatened liver failure which may b precipitated by surgery

A Ryle s tube may offer valuable positive information If the bulb is allowed to pass into the duodenum the aspirated fluid may show the presence of blood suggestive as we have seen of an ampullary site The fluid withdrawn may also be examined for the pancreatic ferments and their absence particularly after a provocative hormone injection is important evidence of blockage of the pan creatic duct

Perhaps the most valuable measure available for the establishment of a diagnosis of obstructive jaundice is liver biopsy by needle puncture In cases in which

jaundice has been present for 3 or 4 weeks the histological picture in the plug of tissue removed will usually serve to distinguish between obstructive jaundice and hepatitis though the histologist will seldom hazard an opinion of whether the obstruction is due to tumour or to stone

DIFFERENTIAL DIAGNOSIS

The differential diagnosis has been largely covered in the consideration of the clinical picture presented by patients suffering from cancer in the region of the head of the pancreas The distinction between carcinoma and hepatitis is not always easy however A long continued jaundice *of a duration of months may* well be due to protracted hepatitis An enlarged gall bladder in these cases is perhaps of more value than anything Jaundice of carcinoma of the pancreas is not always completely progressive as has already been stated but it is seldom so widely variable as it is in hepatitis In many cases the final diagnosis is established only by liver biopsy and in a few unless the gall bladder is palpable as it may not be it may not be clear until operation which of these two conditions is responsible The distinction between cancer of the ampulla of Vater and stone in the common duct is usually relatively easy but less easy than Courvoisier suggested Carcinoma of the pancreas may give rise to pain sometimes severe and occasionally even colicky and intermittent and the gall bladder need not necessarily be palpable even if it is enlarged Similarly in cases of stone pain may be absent usually rather a serious sign and very rarely the gall bladder may even be palpable Radiological examination in these cases is of little advantage for a stone blocking the common duct is seldom seen on the film Only if the shadow of a stone filled gall bladder is visible is the radiological diagnosis absolutely certain It is not the practice to submit jaundiced patients to cholecystography Occasionally a primary or secondary *tumour within the liver obstructing the main hepatic ducts just within the* hilum may closely mimic an obstructive jaundice and give rise to a picture in all respects similar to that presented by a carcinoma lower in the common duct The failure of the gall bladder to enlarge in such circumstances is significant Jaundice of obstructive type may rarely be due to a xanthomatosis of the bile ducts in cases of cholesteraemia This is a good reason for measuring the blood cholesterol and for examining the eyes and the body surface carefully for externally presenting xanthomas The clinical appearances of Hanot s biliary cirrhosis are so identical with those of carcinoma of the ampulla that no distinction can be made between them until operation is done unless the gall bladder is palpable

TREATMENT

All cases of obstructive jaundice should be explored If the cause is stone the stone can of course be removed If the cause is tumour the tumour may be removed or alleviated by a short circuit operation If the obstruction is due to some other cause it is seldom possible to be confident enough of a clinical diagnosis to refuse the patient the hope that operation offers

The preparation includes the administration of vitamin K for a period of some five days before operation and it is usually wise to give this by injection Oral preparations may not be adequately absorbed

The first step of the operation is to verify the diagnosis This is not always easy The normal pancreas is so lobulated a gland that the inexperienced operator can commonly find a cancer where none is present Most ampullary tumours and tumours of the head of the pancreas may be palpated comfortably by inserting the forefinger into the lesser sac and compressing against it the duodenum and head of the pancreas by the thumb held in front of these structures Occasionally in the case of a small tumour it may be necessary to mobilize the duodenum with the head of the pancreas and to feel the head of the pancreas between finger and thumb directly before certainty of diagnosis is reached Even after this manoeuvre a small tumour of the pancreatic duct a few millimetres in circumference may well remain unrecognized but such a tumour will have produced so clear a picture of obstructive pancreatitis with a hard nodular gland that its presence may be deduced Such a condition is nearly always due to a carcinoma of the pancreas duct unless it is clear that pancreatic calculi are present When the tumour is felt an attempt is usually made to remove it It is not always easy to decide at an early stage of the operation whether the tumour will prove to be operable or not It is desirable to take no irretrievable step such as the division of the common bile duct the pancreas or the stomach until operability is certain The head of the pancrea is mobilized widely in the first instance and the uncinate process un hooked from under cover of the mesenteric vessels before the continuity of any of the related ducts is interrupted Sometimes inoperability do s not become manifest until the head is actually being separated from the portal and superior mesenteric veins The relation of the tumour to the hepatic artery too is of some importance A carcinoma high in the head of the gland may encircle this trunk so thoroughly that though easily movable in all other respects the hepatic artery may be sacrificed if the operation is persisted with Division even of the main trunk of the hepatic artery is perhaps of little importance to the normal individual but in a patient who may have a period of low systolic blood pressure after the operation and who during the operation has had the portal vein temporarily compressed while the pancreas is separated from it fatal liver necrosis is almost inevitable if the hepatic artery is divided

Once the growth is found to be operable it must be decided whether to do the operation in one or two stages It is best to warn the patient beforehand that a two stage procedure may be desirable If jaundice is deep and of long standing if the plasma protein is low if the albumin globulin ratio is reversed and if other chemical tests support the suspicion of an impaired liver function of some degree a two stage procedure is unquestionably severe though technically perhaps a little more tedious The most convenient first stage is the performance of cholecystostomy well out in the flank This does not interfere much with the subsequent mobilization of the duodenum and pancreas and it permits the bile to be collected and to be returned to the patient by way of a Ryle s tube

In general the excision of the head of the gland is done by wide mobilization of duodenum and posterior surface of the head as far as the superior mesenteric vein The ligature of Treitz is then divided and the first loop of jejunum is drawn through under the superior mesenteric vessels unhooking the uncinate process Special care must be taken during this stage to avoid a tear in the angle formed between pancreatic veins and superior mesenteric The veins draining the anterior surface

of the head of the pancreas can then be ligated particularly the gastro colic trunk and the veins of the posterior surface of the head are ligated from behind The jejunum is divided beyond the uncinate process and the head is separated from the right border of the mesenterico portal trunk This guides the operator to the space between the neck of the pancreas and the portal vein where the gland can be divided The stomach is transected through the antrum and the bile duct is divided at a high level

There are many possible methods of reconstituting the intestinal tract after this operation and it is of relatively little importance which is employed There are one or two principles which make for safety and comfort however and these include (1) implantation of the cut end of the common duct into the jejunum ligation of the common duct with implantation of gall bladder into intestine is invariably followed by fistula (2) care must be taken to see that the cystic duct joins the common duct above the level of anastomosis or a mucocele of the gall bladder will result if the two ducts are separated to below the level of transection they must be sewn together and the septum between them divided for a little way to form a single tube (3) the cut end of pancreas should be implanted in the small intestine rather than closed off it is always possible to effect an anastomosis between pancreatic duct and jejunum (4) the anastomosis of cut end of stomach to jejunum should be at a level lower than the insertion of the common bile duct and cut end of pancreas or an obstruction may develop at these sites of implantation (5) all these anastomoses are best effected to a loop of jejunum on the distal or left side of the superior mesenteric vessels if the jejunal loop is drawn up to the right of the point where it passes under the mesenteric vessels these vessels may occlude it subsequently

Tumours of the tail and body are more easy to remove than those of the head if they are operable at all They are resected together with the spleen and splenic vessels after mobilization of the gland with the spleen from left to right but it is seldom that the opportunity for this operation arises

Total pancreatectomy has been successfully performed on a few occasions Its mortality is so high and the disability which follows it is so crippling that one wonders whether these patients would not benefit more from a palliative procedure

When the tumour proves to be inoperable relief can of course be obtained sometimes by the performance of cholecystenterostomy or cholecystgastrostomy It is customary to bring up a long loop of jejunum and to unite its summit by anastomosis with the gall bladder also to perform an anastomosis between the two limbs of the loop The addition of gastrojejunostomy to this palliative pro cedure adds very little to the severity of the operation and may prevent the development of the terrible vomiting and duodenal obstruction which sometimes ensues 1–2 years after the performance of cholecystenterostomy

One must refer to a disagreeable predicament in which the pancreatectomist sometimes finds himself There is nothing more humiliating than to explore a patient for proved obstructive jaundice and to find no tumour in the pancreas or common duct a collapsed gall bladder and empty gastro hepatic biliary vessels The diagnosis then rests between Hanot s biliary cirrhosis or some other diffuse intrahepatic obstruction such as xanthomatosis and a liver tumour lying close to the main hepatic ducts and obstructing them It is in this circumstance only that

cholangiography must be performed for the surgeon s peace of mind on the operating table and it is for this reason that surgeons should be prepared for cholangiography at all operations for obstructive jaundice By taking the picture with the patient deep in the Trendelenburg position one can be assured of the level of intrahepatic obstruction If this is proved it i worthwhile to try to dilate the main hepatic ducts within the liver by metal bougies

The post operative course of a patient who has had a cancer of the head of the pancreas resected is in my opinion at least always an anxious one particularly if jaundice has been of long duration before the operation The most serious early complication is anuria and it is known for this to develop in a fatal form in a patient who throughout the operation and for 3 days after it had for her a normal systolic and diastolic pressure At post mortem examination the hepatic arteries and the portal vein were patent yet there was visible necrosis in the liver and in addition a cortical necrosis of the kidney Minor degrees of this syndrome have been more frequent and have impressed upon all the importance of the original description of McFetteridge and Boyce If the output of urine falls in these cases it is usual to treat them as we would a cortical necrosis of the kidney reducing fluids to a minimum and risking dehydration and salt depletion rather than throw upon the kidney a weight of work which it is incapable of supporting

CHAPTER 34

PANCREATITIS

HENRY T HOWAT

PANCREATIC disease presents considerable difficulty to the clinician The pancreas lies deep in the abdomen distant from the palpating hand The gland has no immediate contact with the surface of the body but empties its secretion into an inaccessible part of the bowel Direct biochemical and radiological studies are rarely feasible Frequently the pancreas is not considered to be the seat of disease until contiguous structures such as the common bile duct are involved Frequently too confusion arises in distinguishing between pancreatic disease and disease of neighbouring viscera in particular of the gall bladder The similarity of the symptoms and signs of disease of these two organs is not surprising in view of the close anatomical functional and developmental relationship which exists between the biliary and pancreatic systems Disease of both may coexist but the pancreatic disorder is often overlooked in the presence of the more easily recognized gall bladder lesion

Most authorities on the pancreas stress the need to keep the possibility of pancreatic disease in mind either as a cause or complication of upper abdominal syndromes It is true that the more aware the diagnostician is of the likelihood of disease arising in the pancreas the more often will he interpret correctly the early symptoms of pancreatitis and carcinoma of the pancreas There is a real need for a simple test of pancreatic function which can be applied in these cases before gross pathological changes have occurred in the gland Such a test is not yet available and confirmation of suspected disease of the pancreas can usually only be obtained with considerable difficulty or at laparotomy

During the past decade the study of pancreatic disease has been advanced in four directions (1) the physiologist has elucidated the mechanism of the control of the external secretion of the pancreas (2) pancreatic function tests have been developed which although laborious are sufficiently accurate to be helpful in studying the individual case of pancreatic dysfunction (3) clinical reviews of pancreatitis and carcinoma of the pancreas integrating symptoms with the pathological and biochemical changes which occur have re orientated our knowledge of the development and course of these diseases and (4) technical advances in the surgery of pancreatic neoplasm have provided a stimulus to physician and surgeon alike to recognize the early case which can benefit from radical surgical procedures

PHYSIOLOGICAL ASPECTS

External secretion of the pancreas

When acid chyme passes through the pylorus from the stomach into the duodenum the stimulus is provided for contraction of the gall bladder and the pancreas and intestinal glands secrete These alkaline fluids poured into the duodenum bring

the reaction of the bowel contents to a *p*H more suited to the action of the powerful enzymes liberated into the intestine Trypsinogen the proteolytic enzyme of the pancreatic secretion is activated to trypsin by enterokinase The trypsin formed activates in turn chymotrypsinogen and more trypsinogen Trypsin and chymotrypsin act on native proteins and the degradation products of protein passed on from the stomach to reduce them to easily assimilable amino acids or to simple peptides which are further broken down by carboxy polypeptidases from the pancreas or amino peptidases and dipeptidases in the intestinal mucosa It is well to remember when the action of trypsin is being assessed in duodenal contents that the liberation of a single amino acid which is what is measured is the combined result of the action of the whole proteolytic group encountered in this region

Pancreatic amylase breaks up complex carbohydrates (polysaccharides) into simple diffusible sugars such as maltose The completion of the hydrolysis of the disaccharides maltose sucrose and lactose to the monosaccharides glucose fructose and galactose is accomplished by the three intestinal enzymes maltase sucrase and lactase Pancreatic lipase acts on neutral fats and phospholipids to liberate glycerol and fatty acids The action of bile salts in this regard is important Bile exerts an emulsifying effect on fat entering the intestine and serves as a stabilizer in the fat–water system In addition bile activates pancreatic lipase

Thus on completion of digestion in the upper intestine polysaccharides and disaccharides have been converted into hexoses proteins have been resolved into simple amino acid groups and fat is partly split into separate hydrolytic products It is in these simple forms that the main foodstuffs are absorbed from the bowel and failure of the process of digestion such as occurs after extensive destruction of the pancreas or of obstruction of the pancreatic duct may lead to an increase of nitrogen and fat excreted in the stools Frazer and others (1944) and Frazer and Sammons (1945) have also presented evidence in favour of the absorption of unhydrolysed neutral fat a process which is facilitated by the presence not only of bile salts but of fatty acids and monoglycerides products of lipolysis

Control of external secretion

Though Bernard (1849 1856) and other nineteenth-century physiologists had studied the digestive functions of pancreatic juice it was not till the classical experiments of Pavlov (1902) and of Bayliss and Starling (1902) were published that the basic mechanisms for the production of the external secretion of the pancreas were demonstrated Pavlov who began this work in 1887 showed that stimulation of the vagus nerves in dogs resulted in a flow of pancreatic juice Dolinski (1894) somewhat later proved in the same laboratory that the most powerful secretory stimulant was hydrochloric acid in the duodenum Pavlov who stressed the importance of the nervous control of digestion suggested that hydrochloric acid was a specific excitant of afferent nerve endings in the mucous membrane which formed part of a short excitatory reflex arc to the pancreas The effect could not be mediated by long reflex pathways through the central nervous system for Popielski (1896) in Pavlov s laboratory had shown that section of the splanchnic nerves vagi and spinal cord did not diminish the pancreatic response to hydrochloric acid Wertheimer and Lepage (1901a 1901b) who had

come to a similar conclusion independently went on to show that the response to acid diminished the lower it was introduced into the small bowel (1901c) They could also obtain a response on placing acid in an isolated denervated bowel loop connected to the rest of the body solely by its blood vessels (1901d)

Starting from this last experiment of Wertheimer Bayliss and Starling (1902) who were at that time interested in local motor reflexes of the intestine began an investigation into this alleged local secretory reflex. They repeated and confirmed Wertheimer and Lepage s results It was clear to them that since all nervous connection with the loop had been severed there could be no question of a nervous reflex either central or peripheral but that the connection between the intestinal mucous membrane and the pancreas must be chemical and effected through the blood Hydrochloric acid administered intravenously had no stimulant action on the pancreas They postulated that contact with acid would produce a substance in the intestinal cells which on absorption into the blood stream would stimulate pancreatic secretion Proof of this hypothesis was simple The loop of intestine was cut out and the mucosal cells scraped off and extracted with acid The extract was filtered and injection of the filtrate intravenously produced a copious flow of pancreatic juice This substance formed in the intestinal cells they called secretin

Bayliss and Starling were able to establish the specificity of secretin and showed the absence of action on the salivary and gastric glands Other observers confirmed this work but conclusive proof of the existence of a humoral mechanism was not obtained until Farrell and Ivy (1926) observed secretion of pancreatic juice following a meal from an auto transplant of the tail of the pancreas to the mammary region of a dog The transplant was completely separated from both the nervous and blood supply of the main pancreas In the same dog they were able to elicit secretion from the transplant when weak hydrochloric acid was introduced into trans planted jejunal loops (Ivy Farrell and Lueth 1927)

Bayliss and Starling (1902) claimed that the hormonal mechanism mediated by secretin was adequate to account for the secretory activity of the pancreas and cast doubt upon the importance or even existence of a nervous control of the gland Though there was some basis for Bayliss and Starling s criticisms of Pavlov s early experiments the presence of secretory and trophic fibres to the pancreas in the vagus nerves was later confirmed by many workers with improved techniques (Anrep 1916 Tonkich 1924 Baxter 1931 Crittenden and Ivy 1937)

The contradictory views of Pavlov and Bayliss and Starling were seemingly reconciled when Mellanby (1925) published his work on cats He showed that secretin was responsible for the output of water and bicarbonate in pancreatic juice but that the enzyme content was determined by the vagal nerves Stimulation by pilocarpine increased the enzyme concentration of the juice Vagotomy and atropine were found to reduce the enzyme output but did not alter the response to secretin Thus it seemed clear that pancreatic secretion was regulated by both nervous and hormonal influences This dual hypothesis has been widely held till recent years

Several later observers however found that preparations of secretin would stimulate the output of enzymes To study this and other discrepancies Harper and Vass (1941) undertook an investigation in cats They showed that the passage

of foodstuffs normal saline or water through the pylorus into the duodenum resulted in an increase in enzyme output by the pancreas and in most cases an increase in the rate of secretion This increase in enzyme output could be observed after all the extrinsic nerves of the small intestine had been cut and was not prevented by the exclusion of acid and bile from the intestine These observations could not be reconciled with Mellanby s sharp demarcation of hormonal and vagal control Harper and Vass confirmed however that secretin extracts prepared by Mellanby s method did not increase enzyme output and that in the cat vagal stimulation had no effect on the rate of secretion but produced a parallel increase of the enzymes trypsinogen and amylase

These apparent anomalies were explained when Harper and Raper (1943) were able to isolate from the small intestine of several species a substance distinct from

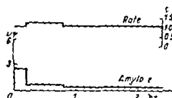


FIG. 264.—Action of secretin on the external secretion of the pancreas of the cat Secretin injected intravenously every 12 minutes throughout the experiment resulted in a flow of juice of low enzyme content (The rate of flow is expressed in cc per 12 minutes D^J_T is the minute output of amylase) (Harper and Mackay 1948) (*By courtesy of Journal of Physiology*)

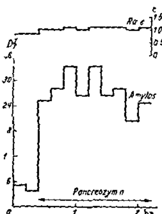


FIG. 265.—Action of pancreozymin on the external secretion of the pancreas of the cat In addition to secretin given to maintain the flow of pancreatic juice intravenous pancreozymin was given every 12 minutes during the period indicated by the arrows A sustained rise in output of amylase resulted (Harper and Mackay 1948) (*By courtesy of Journal of Physiology*)

secretin which on intravenous injection in cats caused an increased secretion of enzymes by the pancreas but had no effect on the volume of juice secreted (*see* Figs 264 and 265) The response of the pancreas was unaffected by section of the vagus and splanchnic nerves or by the administration of atropine They called the substance pancreozymin and suggested tentatively that it might be a hormone released by the mucosa on contact with acid and foodstuffs This would explain the increase in enzyme content found by Wang and Grossman (1950) following

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the giving of meals to dogs with the pancreas transplanted under the skin The presence of pancreozymin in extracts of duodenal mucosa was quickly confirmed by Greengard Grossman Woolley and Ivy (1944) Harper and Mackay (1948) showed that pancreozymin could produce a depletion of the zymogen granules in the acinar cells comparable to that caused by vagal stimulation

The action of the splanchnic nerves on pancreatic secretion is controversial Taking into consideration the varying results in different species of experimental animals the known facts are best explained by assuming that the inhibitory action of splanchnic stimulation is mediated solely by the constrictor effect of these nerves on the splanchnic vessels

Summary —Animal experiments have shown that the external secretion of the pancreas is regulated by a dual hormonal and nervous mechanism Contact of acid and food with the upper intestinal mucosa probably releases from the mucosal cells secretin and pancreozymin Secretin produces a large volume of juice of considerable alkalinity but low in enzymes pancreozymin increases enzyme output The effect of vagal stimulation on the volume of the juice varies in different species but in all it increases the output of enzymes Physiological opinion agrees it is likely that the intestinal phase of pancreatic secretion is the important one there is little evidence of a cephalic phase of pancreatic secretion in any way comparable to that of gastric secretion The role played by the vagus physiologically is therefore obscure

Internal secretion of the pancreas

That the pancreas has other than digestive functions has been recognized since the fundamental discovery of Minkowski (1889) and von Mering and Minkowski (1890) that total pancreatectomy was followed by glycosuria and other metabolic disturbances which strikingly resembled diabetes mellitus in man When it was perceived that after ligation of the pancreatic ducts the islets of Langerhans were preserved it was presumed that the islet cells were the source of a hormone The isolation of insulin by Banting and Best (1922) from the pancreas of dogs after previous duct ligation proved the soundness of this hypothesis In diffuse pancreatic lesions hyperglycaemia and glycosuria may not be infrequent clinical findings

Lipotropic factors of the pancreas

Allan Bowie Macleod and Robinson (1924) and Fisher (1924) reported that depancreatized dogs kept alive by insulin developed a massive fatty infiltration of the liver This might be associated with a fall in plasma lipids The feeding of raw pancreas or of lecithin would inhibit these changes It was soon appreciated that the lipotropic action of lecithin was due to its choline component and that the similar action of methionine was due to the ability of the methionine to supply labile methyl groups essential for the synthesis of choline It was shown however that the daily ingestion of small amounts of pancreas or of pancreatic juice sufficient to prevent fatty livers could not be accounted for by their choline content Dragstedt and others (1936 1939) obtained an alcohol extract of pancreas which contained a substance named by them lipocaic which they considered to have the attributes of a hormone This material when given by mouth or

subcutaneously prevented the development of fatty livers in depancreatized dogs Entenman Chaikoff and Montgomery (1944) have also prepared an anti fatty liver factor from the pancreas There is some evidence that thes factors are not identical It is said by Chaikoff that choline is bound to phospholipid in plasma and that the plasma phospholipid level is a measure of its choline content If this is true it seems likely that these pancreatic factors which inhibit a fall in plasma phospholipid and fatty infiltration of the liver may be concerned with the metabolism of choline Despite much experimental work the relationship of these factors to each other their specificity and connection with the avail ability of free choline are not known The reader is referred to recent reviews for a bibliography (McHenry and Patterson 1944 Best 1948 and Chaikoff and Entenman 1948)

PANCREATIC FUNCTION IN MAN

In man pancreatic function has been studied by two methods The first of these is the collection of pancreatic juice from fistulae the sequel to op ration for pancreatic pseudocysts following trauma or pancreatitis Fistula juice may give some indication of pancreatic function though there is no doubt that the pancreas is abnormal in such cases The juice is also liable to early contamination by micro organisms with a resulting destruction of the enzymes

The second method has been that of duodenal intubation This also has not proved entirely satisfactory (The duodenal contents are an admixture of fluid from the stomach biliary tract intestine and pancreas) Moreover the stimulants used in many of these experiments have not been standardized Sampling of duodenal contents after the introduction of food food digests or hydrochloric acid can give only roughly quantitative results Vagal stimulants when used produce conflicting results This is probably due to the fact that vagal stimulants in addition to other side effects stimulate the secretion of hydrochloric acid in the stoma h If precautions are not taken to prevent the passage of this acid into the duodenum accurate and quantitative results are not obtained

Chiray Salmon and Mercier (1926) and Chiray Jeandel and Salmon (1930) were the first workers to use secretin as a stimulant of pancreatic juice in man Their methods were followed by Bolgert (1935) in Chiray s clinic and by Voet (1943) of Courtrai Voegtlin Greengard and Ivy (1934) also used secretin to stimulate pancreatic flow in man but found that their preparation produced untoward anaphylactic effects It was left to the Swedish group of workers to elaborate a technique by which accurate quantitative obs rvations could be made

Being in possession of a purified secretin preparation Ågren and Lagerlof developed a method by which it could be used in man Lim Matheson and Schlapp (1923) in Shafer s laboratory in Edinburgh had first used two separate *Einhorn* tubes one in the stomach and the other in the duodenum to obtain pure samples of gastric and duodenal juice Ågren and Lagerlöf (1936) made use of the same principle in constructing a double lumen tube one passage ending in the duodenum the other in the stomach A functional separation of stomach contents from duodenal contents is thu assured at the pylorus and quantitative recovery

the giving of meals to dogs with the pancreas transplanted under the skin The presence of pancreozymin in extracts of duodenal mucosa was quickly confirmed by Greengard, Grossman Woolley and Ivy (1944) Harper and Mackay (1948) showed that pancreozymin could produce a depletion of the zymogen granules in the acinar cells comparable to that caused by vagal stimulation

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The concentration of amylase trypsin and lipase drops to a low level in the second 10-minute period after which it rises as the rate of secretion of juice falls The total amounts of enzyme secreted per unit time are of the same magnitude in the different samples with the exception of the first 10-minute sample (Fig 267) In the first 10 minute sample after secretin the concentration of the three enzymes rises in parallel fashion The total output is much increased and the parallelism exists in total output of all three enzymes following secretin This parallel increase is noted in animal experiments following electrical stimulation of the vagus or secretin and pancreozymin stimulation

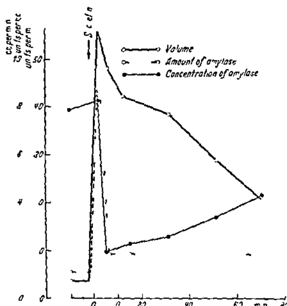


Fig 267—The secretin test in man Rate of secretion concentration and total output of amylase in response to secretin (mean of 13 experiments) (Lagerlöf 1942) (*By courtesy of Acta Medica Scandinavica*)

At first Ågren and Lagerlöf (1936) concluded that secretin stimulated the flow of enzymes Lagerlöf (1942) later revised this idea and concluded that the rise in the first period following secretin was due to the dead space in the tube and bowel an error inherent in the method It may be partly explained in this way and partly be due to a washing out of pre formed enzymes by secretin stimulated juice a phenomenon noted in animals Voegtlin Greengard and Ivy (1934) concluded that secretin stimulated a flow of enzymes An additional factor in their experiments would be that their secretin contained pancreozymin The secretin test when repeated in the same individual gives repeatable results so far as volume and bicarbonate are concerned Greater variation in enzyme content occurs

Lagerlöf (1942) in his monograph gives quantitative values for total volume bicarbonate output and output of enzymes in the duodenal contents following stimulation by secretin The figures for volume and bicarbonate have been corrected to compensate for deterioration of the secretin unit for the secretin

of gastric and duodenal contents is obtained by aspirating both tubes under a constant negative pressure of 20–30 millimetres of mercury The duodenal contents are collected in ice cooled flasks containing glycerin to prevent inactivation of lipase and trypsin Saliva is also aspirated from the mouth Preventing the passage of hydrochloric acid into the duodenum by continuous gastric aspiration obviates the stimulant action of the acid on the pancreas and the neutralization of the bicarbonate secreted into the duodenum It may be argued that bile and intestinal juice are present but in practice the errors due to these substances are minimized when quantitative recovery of duodenal contents is achieved These workers were also the first to use a potent pure secretin which had no disturbing side effects on man

The secretin test is carried out on fasting subjects After a control period of usually 20–40 minutes secretin is injected intravenously The duodenal and gastric contents are collected in 2 10 minute and 2–3 20 minute fractions The volume of secretion of pancreatic juice following secretin given intravenously reaches its maximum in 10 minutes and then diminishes The dose used (1 clinical unit per kilogram of body weight) affects the secretion for over an hour The mean volume of duodenal contents secreted in 60 minutes in response to this dose of secretin was 202 5 millilitres in Lagerlof s series of 48 healthy adults (1942) In man as in animals secretin stimulates the secretion of a juice with high bicarbonate and a low chloride concentration When secretion reaches its peak the concentration of bicarbonate in the duodenal contents is about 125 milli

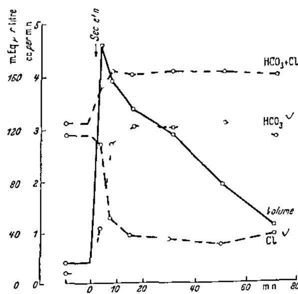


Fig 266 —The secretin test in man Rate of secretion and concentration of bicarbonate and chloride in response to secretin (Lagerlof 1942) (*By courtesy of Acta Medica Scandinavica*)

equivalents per litre and chloride about 30 milliequivalents per litre The concentration of bicarbonate diminishes as volume diminishes and the concentration of chloride rises inversely (Fig 266) The sum of the concentration of bicarbonate and chloride is about 155 milliequivalents per litre The mean total output of bicarbonate in 60 minutes was 19 38 *milliequivalents in* Lagerlof s normal series

The concentration of amylase trypsin and lipase drops to a low level in the second 10-minute period after which it rises as the rate of secretion of juice falls The total amounts of enzyme secreted per unit time are of the same magnitude in the different samples with the exception of the first 10 minute sample (Fig 267) In the first 10-minute sample after secretin the concentration of the three enzymes rises in parallel fashion The total output is much increased and the parallelism exists in total output of all three enzymes following secretin This parallel increase is noted in animal experiments following electrical stimulation of the vagus or secretin and pancreozymin stimulation

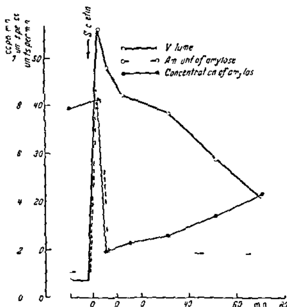


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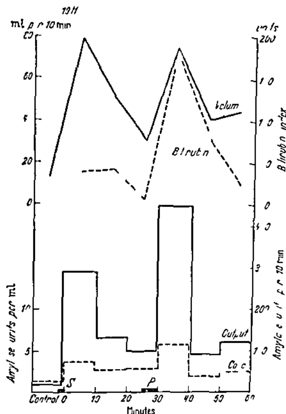


FIG. 268.—The secretin pancreozymin test in man. Volume of duodenal contents, bilirubin concentration, concentration and total output of amylase in response to secretin (S) and pancreozymin (P).

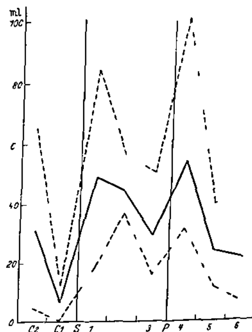


FIG. 269.—The secretin pancreozymin test in man. Volume of duodenal contents in millilitres per 10-minute period (mean and range of 8 experiments).

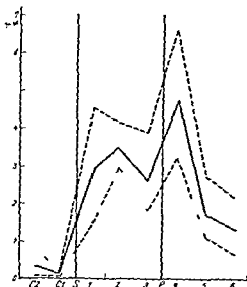


Fig. 270.—The secretin pancreozymin test in man. Total output of bicarbonate in millimols per 10-minute period (mean and range of 8 experiments)

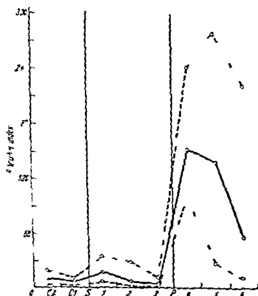


Fig. 271.—The secretin-pancreozymin test in man. Bilirubin concentration (mean and range of 8 experiments)

used by him lost about 15 per cent of its potency in 12 months Diamond and Siegel (1940) have expressed their results in *terms of output per kilogram of body* weight

Secretin has also a choleretic effect In patients with a non functioning gall bladder or following cholecystectomy the samples of duodenal juice following *secretin are uniformly stained with bile In normal subjects however the liver* bile is taken up by the gall bladder for a certain time After secretin the bilirubin index of succeeding samples diminishes or may be absent in one or other of successive samples to reappear in later fractions as the gall bladder is distended (*Ågren and Lagerlöf 1937 Diamond Siegel and Myerson, 1940b*) *This* capacity for receiving bile is used as a test of function of the gall bladder (Fig 275)

Confirmation of the results obtained in man by this secretin test have come from many sources particularly in America (Diamond Siegel Gall and Karlen,

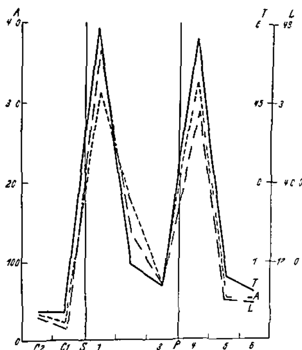


Fig 272—The secretin pancreozymin test in man Total output of amylase trypsin and lipase (mean of 6 cases)

1939 Comfort and Osterberg 1940a Pratt Brugsch and Rostler 1940 Pollard *Miller and Brewer* 1942 Lake 1947 and Dreiling and Hollander 1948 1950)

A group of workers in Manchester have obtained pancreozymin sufficiently pure to use in man Their preparations of pancreozymin contain a substance which causes contraction of the gall bladder in cats This is possibly cholecys*tokinin* Recently a preliminary report has been given by the Manchester workers on the use of pancreozymin in combination with the secretin test (Duncan Harper Howat Oleesky and Varley 1950) Their technique closely follows that of the Swedish workers but they use two tubes one lying in the duodenum and *the other* in the stomach Tests are made on fasting subjects and the duodenal contents are collected in 10-minute samples Thirty minutes after the secretin

injection an intravenous injection of pancreozymin is given. After the injection of pancreozymin the output of juice is raised (Figs 268–271). As seen from the colour of the juice and the bilirubin index this is due to contraction of the gall bladder. The bicarbonate concentration falls as does the pH of the fluid. Following pancreozymin there is a parallel increase in the three enzymes (Fig 272). They have thus confirmed that the action of pancreozymin in man is similar to that found by Harper and Raper (1943) and Harper and Mackay (1948) in the cat. This extract appears to act as a specific enzyme stimulant.

Summary.—The fluid bicarbonate and enzyme output of the pancreas have been assessed in man by aspirating duodenal contents according to the technique of Ågren and Lagerlöf. Considerable variation exists in the fasting state but the results are more consistent when the gland is stimulated to secrete. The response of the normal pancreas to standard intravenous injections of secretin has been measured by several workers. By using this method it is known that the effects of secretin and pancreozymin on man are the same as those observed on animals.

TESTS OF PANCREATIC FUNCTION

Functional tests play an important part as an adjunct in the diagnosis of pancreatic disease. These tests depend on (a) estimation of enzymes in serum or urine and (b) estimation of pancreatic external secretion in duodenal contents.

The former are much more popular in routine clinical work largely because of the ease of estimation. The great drawback to their use is the wide range of enzyme levels which may be found in a group of normal individuals. Considerable dysfunction may be present before abnormal values are encountered.

Serum amylase

The two main methods employed to measure serum amylase are the amyloclastic method of Wohlgemuth as modified by Somogyi and the saccharogenic method of Somogyi (1938). The first measures the initial stages of breakdown of starch to erythrodextrins, the second is an estimation of the amount of reducing substance liberated in more complete starch digestion. In practice the two methods show close parallelism though the second is more precise (Somogyi 1932, 1931–32). Laboratories, however, should be familiar with both techniques for the saccharogenic method becomes more liable to error when there is hyperglycaemia and the amyloclastic technique may give fallacious results in the presence of jaundice. Both states are not uncommon in pancreatic disease. In some laboratories the normal values given by Somogyi (1941) for the saccharogenic method have not been confirmed. In our experience value of 30–125 milligrams of reducing substance expressed as glucose per 100 millilitres of serum is the normal range. Comparison of values from different laboratories is difficult and workers using the same methods may adopt a different range of normal values.

Amylase is present in blood serum in man in health. A proportion of this may have its origin in the liver but the major portion arises from the pancreas. A diminished value is found in liver disease and after pancreatic ablation (Somogyi 1934–35). Enzyme levels in the portal vein and pancreatic vein are higher than levels in peripheral veins following pancreatic trauma (Howard, Krehl, Smith and

Peters 1949) An elevated value follows absorption of amylase into the blood stream from the acini or ductules of the pancreas and is found in pancreatitis and obstruction of the duct (Fig 273) The cause of this obstruction is not revealed by this functional test A raised serum amylase will only be found in pancreatic disease if the acinar cells are functioning

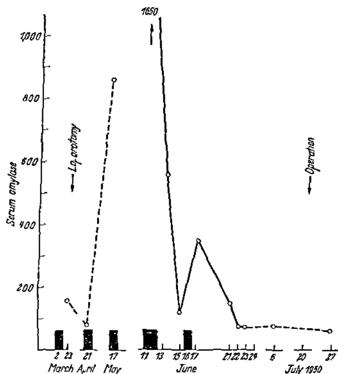


Fig 273—Acute recurring pancreatitis Serum amylase values recorded during 5 episodes of upper abdominal distress

Certain diseases apart from disease of the pancreas may cause a rise in serum amylase for instance mumps and suppurative parotitis The diagnosis is as a rule *clearly established in these cases by inspection Serum amylase values also rise in* renal failure with nitrogen retention Recently in a few cases of abdominal disease in which the pancreas was not primarily involved—perforation of peptic ulcer small gut obstruction and peritonitis—elevated values have been recorded (Raffensperger 1950) These were present several days after the onset of symptoms and the presumption is that in these cases an increased back pressure had been produced in the pancreatic duct In none of these cases did the serum amylase exceed 500 milligrams These occasional findings may possibly be attributable to *spasm of the sphincter of Oddi following the use of opium derivatives in treatment* Gross Comfort Mathieson and Power (1951) have recently reported a rise in serum amylase in a few cases of biliary dyskinesia to whom codeine had been given

In pancreatic disease serum amylase estimations have proved of more value in the diagnosis of *acute pancreatitis at an early stage of the disease than in chronic* disease Values greater than 500 milligrams in the presence of acute symptoms

referred to the upper abdomen are almost pathognomonic of acute pancreatitis The rapidity of obstruction may b important Early and repeated estimations should be made so that a transient rise in level may not be overlooked A fall in serum amylase during acute pancreatitis does not necessarily mean that improvement is taking place it may represent a destruction of functioning acinar tissue by the disease process It must not therefore be used as a prognostic test

In more chronic pancreatic disease either inflammatory or neoplastic the serum amylase *does not rise* so dramatically Evidently here the obstruction is more gradual or the functional activity of the gland diminishes *pari passu* with the obstruction The serum amylase however gives a comparatively constant value for the individual (Elman Arneson and Graham 1929) If the base line value for the individual is known a comparatively small elevation may prove significant and may be helpful in elucidating symptoms produced by disease in the upper abdomen

Urinary amylase

Urinary amylase has long been a popular test with British surgeons in acute pancreatitis Normally the urine concentrates the amylase of the serum In acute pancreatitis the concentration ratio persists and as the urinary amylase may remain higher for some hours longer than the serum amylase urinary values may be the test of choice at a later stage of the disease The estimation should be made on 24-hour samples of urine as fluctuations may occur in single samples due to dehydration or diuresis In renal failure this test may give low values (Gray and Somogyi 1937 Huggins and Russell 1948)

Serum lipase

In man there is probably little lipase of pancreatic origin present in serum though serum contains esterases capable of acting on the organic esters of fatty acids of low molecular weight In pancreatic disease however pancreatic lipase may enter the blood stream The distinction between serum lipase and serum esterase is not absolute Lipase hydrolyses the esters of higher fatty acids preferentially whereas esterase acts on the esters of short chained fatty acids Since a considerable overlap exists in the action of the two enzymes attempts have been made with inhibitors and potentiators to increase the specificity of the tests for pancreatic lipase present in serum in pancreatic disease (Chiray Berdet and Taschner 1931 Lagerlöf 1945 1947) Lagerlof suggests that for diagnostic purposes the definition of pancreatic lipase in serum should be limited to the atoxyl resistant esterase which is activated by the addition of calcium oleate

In clinical practice the method used by most workers is a modification of the Loerenhart technique for esterase described by Cherry and Crandall (1932) The substrate is olive oil and in spite of the theoretical disadvantages of a reaction taking place in a two phase oil and water system it proves a satisfactory clinical test In our experience the replacement of olive oil by other substrates such as the simpler esters of fatty acids is of no advantage In the Cherry and Crandall method the serum and olive oil are incubated for twenty four hours which limits the value of the test in acute pancreatitis No other simple rapid and accurate method of estimating pancreatic lipase however has yet displaced this

method in clinical laboratories Values which exceed 1 5 millilitres of N/20 sodium hydroxide are considered abnormal

In pancreatic disease serum lipase varies with serum amylase though they do not run wholly parallel courses The estimation of serum amylase because it can be done more rapidly is the method of choice in acute pancreatitis though the serum lipase may be elevated in a higher proportion of cases (Comfort and Osterberg 1940b) The elevation of serum lipase may be delayed a little and may be present longer than the rise in amylase (Johnson and Bockus 1940) Elevated values have been reported by Raffensperger (1950) in a few instances of perforated ulcer, intestinal obstruction and peritonitis not primarily due to acute pancreatitis and by Gross Comfort Mathieson and Power (1951) in biliary dyskinesia following the administration of opium derivatives

Serum lipase is more often raised in cancer of the pancreas and cancer of the ampulla of Vater than is serum amylase (Comfort and Osterberg 1940b) Johnson (1950) suggests that a high value is not found till the region of the main pancreatic duct is involved in the tumour Repeated tests should therefore be made in these cases for normal values do not exclude the presence of pancreatic disease A fall in serum lipase may accompany the late stages of carcinoma with destruction or atrophy of acinar tissue

Summary —Estimation of the serum enzymes can establish the diagnosis of acute pancreatitis A raised value for serum amylase is particularly useful in differentiating acute upper abdominal conditions for the test can be completed within an hour Sometimes the rise is missed or absent occasionally a raised value is found in other conditions The limitations of the tests must be taken into consideration when their significance is assessed in the individual The best guide is obtained by correlating the laboratory tests with the clinical state of the patient

Serum enzymes following stimulation of the external secretion

The estimation of the serum enzymes in acute pancreatic disease is of such value that many workers in this field have modified the conditions of the tests to increase their value especially in carcinoma of the pancreas and in chronic and inter mittent forms of pancreatitis This has been done in 3 ways (1) by stimulating the pancreas to secrete (2) by giving morphine which produces spasm of the sphincter of Oddi thus increasing the obstruction in the duct system (Lagerlöf 1945) and (3) by combining these two methods

The pancreatic stimulants used have been as a rule secretin and parasympatho mimetic drugs Popper and Necheles (1943) showed experimentally that secretin and mecholyl produced an elevation of serum lipase in dogs with a normal pancreas but not in animals in which the pancreas had atrophied Secretin alone would produce no elevation in normal dogs but a rise was found after the pancreatic duct was tied (Popper Olson and Necheles 1943)

These observations suggested the two ways in which serum enzyme estimations following stimulation of the pancreas might be adapted for clinical use in man

Serial determinations of serum enzymes following maximal stimulation of the pancreas

In this method a powerful stimulus is given to cause a maximal response from the gland When acinar function is normal a rise in serum enzymes would be

found but no elevation would occur in the presence of severe acinar destruction In clinical practice this sharp distinction is not always observed in individual cases In a recent paper Myhre Nesbitt and Hurly (1949) described their results when they used secretin combined with 20 milligrams of mecholyl chloride or with morphine to cause maximal secretion A significant elevation of serum amylase or lipase was found in 70 per cent of normal subjects The morphine secretin test gave no rise in nine patients with advanced pancreatic disease The percentage of positive tests is not sufficiently high to justify the use of this technique in clinical practice There seems little point of applying these tests to prove the destruction of pancreatic acinar tissue This is as a rule recognized clinically by stool examination and with much more certainty by examination of the duodenal contents after stimulation of the pancreas as described below Burke Plummer and Bradford (1950) moreover doubted the wisdom of combining the action of morphine with secretin in cases of pancreatitis

Serial determination of serum enzymes following submaximal stimulation of the pancreas

By the alternative method a milder stimulus is given since the purpose of the test is different A submaximal response from the normal pancreas would cause no elevation in serum enzymes but in the presence of duct obstruction a rise would be obtained Knight Muether and Sommer (1949) who did serial determinations of serum amylase at intervals of 30 minutes following 1 milligram of Prostigmin methylsulphate intramuscularly have analysed the changes observed over 2 hours Normal cases showed no alterations In obstruction of the duct and in destruction of the gland characteristic deviations are obtained Though their interpretation of the group results is instructive in most cases the response of the individual patient suffering from chronic pancreatitis is not decisive enough to be of diagnostic value It would appear that the dose of Prostigmin used does not stimulate the external secretion of the pancreas sufficiently to achieve the aim of the test Moreover vagal stimulants are not the best to use for this purpose since they may both have a direct action on the pancreas and a secondary action on the pancreas through the stimulation of gastric secretion and the subsequent passage of hydrochloric acid into the duodenum

Lopusniak and Bockus (1950) in a recent study in which secretin only was administered did serial estimations of serum amylase and lipase before and 1 4 and 24 hours after giving the hormone In a control group no elevation of serum enzymes occurred but in cases of pancreatitis in which high initial enzyme values had been observed and in cases examined within 10 weeks of an acute attack elevation occurred after secretin In pancreatitis and carcinoma of the pancreas with normal fasting values a rise in enzymes was not often seen

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This field is an important one because of the technical simplicity of these tests

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This field is an important one because of the technical simplicity of these tests

Much more work must be done to determine the optimal dosage of stimulant material *The optimal dosage is one which gives* no rise in the normal individual but produces a significant rise when some obstruction is present in the duct system It must be remembered that such a test is only of value as a test of existing conditions and if no obstruction remains when the pancreatitis subsides then no elevation of serum values occurs When the acinar function of the gland is destroyed the values will remain low even in the presence of gross pathological change In these cases however the pre stimulation values may be low Secretin seems to be an appropriate stimulant As a concomitant pancreozymin has many points to recommend it *since it appears* to be a specific enzyme stimulant and does not have a secondary action upon gastric secretion Incidentally *it is important* in evaluating papers on this work to know if the secretin preparations used contained pancreozymin

Duodenal contents following stimulation of the pancreas

Tests can be made directly on duodenal contents after stimulation of the pancreas The technique of Ågren and Lagerlof is used and secretin is given as a stimulant By this method direct evidence can be obtained of the integrity of the pancreas The work of early pioneers of this method is criticized on the ground of imperfect technique and impure secretin The Astra secretin however used by recent workers contains no pancreozymin

In the doses used by Lagerlof secretin produced an almost maximal rate of pancreatic secretion In pancreatic disease Lagerlof (1942) classified his results as follows

Type I—Usually follows acute pancreatitis The enzyme secretion is depressed The characteristic finding is a reduction in the amount of amylase while values *for trypsin* and lipase *may* fall within normal range This state is reversible

Type II—Occurs in pancreatic disease where irreversible injury has taken place as a result of necrosis fibrosis tumour or duct obstruction In this case a *fall in both enzyme and bicarbonate output occurs*

Transitional types also occur

A reduced volume of the duodenal contents following stimulation by secretin is not such a characteristic *feature* of *pancreatitis* as *a lowered* output of bicarbonate This Lagerlöf (1942) attributes to a depression of gall bladder function in pancreatic disease Hepatic bile flows more or less continuously in these cases to augment the duodenal juice but *bile does not raise the bicarbonate values to the same extent* In cancer of the head of the pancreas however which is involving the common bile duct and main pancreatic duct a reduced volume accompanies the fall in output of bicarbonate and enzymes *According to Dreiling* and Hollander (1948) the lowering of the volume response is more characteristic of malignancy in contrast to chronic pancreatitis in which the concentration values for bicarbonate and enzymes are low The ductal obstruction is *the primary* physiological disturbance in carcinoma though acinar cell damage may occur later

The dissociation of the enzymes seen in the type I group has *also been* described in pathological cases by Diamond and others (1939 1940 1941) who have reported extensively on the secretin test Comfort and Ost rberg (1941)

investigated the merits of different pancreatic stimulants and came to the conclusion that mecholyl chloride and secretin have distinct advantages over food and other stimulants Mecholyl had the advantage of being an enzyme stimulant A combination of both provided a powerful stimulus of volume bicarbonate and enzymes A disadvantage is the increased risk of contamination of duodenal contents with hydrochloric acid

Dornberger Comfort Wollager and Power (1948) recently performed secretin tests on 28 cases of chronic relapsing pancreatitis and compared the data with those from 11 normal persons This is the largest pathological group studied as yet and their careful analysis of data and assessment of the secretin test are most valuable The values for volume of duodenal contents concentration of bicarbonate and total bicarbonate disclosed insufficiency of external pancreatic secretion in all of 16 cases with extensive parenchymal destruction (indicated by calcification diabetes and steatorrhoea) of 12 cases of chronic pancreatitis without these criteria of extensive damage these values disclosed disturbance in 7 cases Analysis for total enzymes revealed dysfunction in only 2 or 3 cases They concluded that the secretin test has a definite but limited place in the diagnosis of pancreatitis that it might well be limited to determinations of volume bicarbonate concentration and output and that enzyme estimations did not add to the value of the test

The recent use of pancreozymin in conjunction with the secretin test suggests that further experience should be sought with this enzyme stimulant It is suggested from preliminary work that increased reliance can be placed on enzyme values secured by this hormone (Fig 274)

Use of secretin to test gall bladder function

In addition to their use as stimulants of the pancreas secretin and pancreozymin may be of value as tests of gall bladder function Secretin has a choleretic action and according to Ågren and Lagerlof (1937) and Diamond Siegel and Myerson (1940b) the biliary pigment concentration in duodenal contents gives characteristic curves in response to secretin It is possible to distinguish between three types of response (Fig 275)

Type I Normal response—The gall bladder is capable of receiving and concentrating bile flowing from the liver and the sphincter of Oddi is competent The bilirubin index of the duodenal contents falls even to zero in the second or third samples but a rise takes place in later samples as the gall bladder fills to capacity

Type II Non functioning gall bladder or following cholecystectomy—A continuous flow of bile passes through the incontinent sphincter of Oddi The fall in the bilirubin index is a result of the dilution of the bile by pancreatic and intestinal juice

Type III Complete biliary obstruction—Bile pigment is practically absent throughout the test

Recently Dreiling and Hollander (1948) and Dreiling (1950) have described a Type IV response occurring in patients whose gall bladder has been removed This is intermediate between Type II and I and in these subjects the common bile duct may be dilated and is taking on the function of a biliary reservoir The

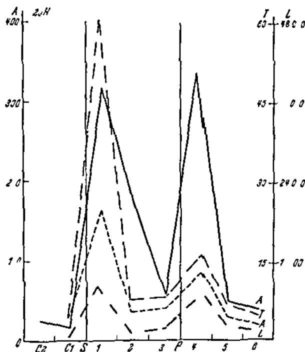


FIG 274 —The secretin pancreozymin test in chronic pancreatitis Total output of amylase trypsin and lipase In this patient the volume of duodenal contents was within normal limits but the bicarbonate output was reduced (The continuous line represents the mean amylase output of normal subjects—*see* Fig 272)

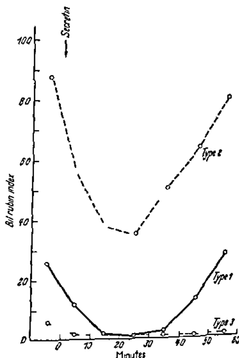


FIG 275 —The secretin test in man Bilirubin excretion (Ågren and Lagerlof 1937 Diamond Siegel and Myerson 1940b) (*By courtesy of American Journal of Digestive Diseases and Acta Medica Scandinavica*)

condition is associated with incomplete biliary obstruction either by stone stenosis or post-operative stricture

Pancreozymin preparations contain a substance possibly cholecystokinin which causes a contraction of the gall bladder in anaesthetized cats and in man We have found in using the secretin pancreozymin test that this response gives additional information of the integrity of the gall bladder (Fig 271)

Summary —The tests in which the duodenal contents are analysed and the serum enzyme levels determined after the giving of secretin and pancreozymin are of considerable importance in affording direct information about the function and integrity of the pancreas at the time of the test They are applicable to the more chronic forms of pancreatic disease and are particularly useful in (1) the diagnosis of pancreatic destruction (2) the diagnosis of chronic relapsing pancreatitis (3) the diagnosis of carcinoma of the head of the pancreas (4) the differential diagnosis of cases of jaundice and (5) the differential diagnosis of cases of steatorrhoea The gall bladder test with the same stimulants forms a useful adjunct to the pancreatic tests

It is unfortunate that intubation of the duodenum and analysis of the duodenal contents is so laborious and time-consuming This method is thus not likely to find a place in routine diagnostic methods of upper abdominal syndromes The serum enzyme determinations after the giving of pancreatic stimulants are a much more practical project It is doubtful if the optimal stimulant or dosage has been found for this purpose

Examination of stools

Indirect methods are also used to demonstrate deficiency of the external secretion of the pancreas Undigested meat fibres and fat may be found in the stools in advanced cases of chronic pancreatitis Qualitative changes in the naked eye and microscopic appearances of the faeces are less dependable characteristics than quantitative evidence which is obtained by correlating the faecal output with the dietary intake of fat and nitrogen Analysis of the faeces for total fat gives earlier information in the diagnosis of pancreatic disease than an analysis for total solids or faecal nitrogen (Dornberger Comfort Wollager and Power 1948) These workers gave a 2 463 calorie diet which contained an average daily intake of 101 6 grams of fat 117 6 grams of protein (18 8 grams of nitrogen) and 269 6 grams of carbohydrate In normal persons the range of average daily loss of faecal fat varied from 1 8–6 7 grams and the average daily faecal nitrogen varied from 0 8–2 5 grams (Wollager Comfort and Osterberg 1947) Fat balance studies with different dietary intakes have yielded comparable values (Black Bound and Fourman 1947 Cooke Elkes Frazer Parkes Peeney Sammons and Thomas 1946) When a patient on a daily intake of 100 grams of fat excretes more than 10 grams of fat in the stools deficiency of fat absorption is present If pancreatic deficiency is responsible for the excessive loss the pancreatic damage is roughly proportional to the output of fat in the stools (Dornberger Comfort Wollager and Power 1948)

The rapid method of estimating faecal fat described by van de Kamer Huinink and Weyers (1949) is now used The method was suggested by Professor A C Frazer of Birmingham Daily estimations of faecal fat are made If the results indicate

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the presence of steatorrhoea the fat balance studies need only continue for a few days if however the results are equivocal the studies should continue for a period of 12 days to permit statistical evaluation of the data When steatorrhoea is demonstrated the stools may be further analysed for unsplit and split fat An excess of neutral fat indicates failure of fat digestion The differentiation, however of pancreatic steatorrhoea and steatorrhoea due to defective absorption of fat can be made more readily on other criteria such as episodes of pain calcification or diabetes excessive loss of nitrogen in the stools or by more direct methods of proving pancreatic insufficiency such as the secretin test (Comfort Dornberger Wollaeger and Power 1949)

Deficiency of internal pancreatic secretion

Diffuse lesions of the pancreas may lead to impaired function of the islet cells Acute attacks of *pancreatitis are accompanied by hyperglycaemia or glycosuria* more frequently than is appreciated The disturbances of insulin production *is sometimes mild and transient* and may be overlooked unless a glucose tolerance test is made A permanent diabetes mellitus may result from a severe attack of acute pancreatitis but remarkable recovery can take place in the weeks and months which follow resolution of the inflammatory process Diabetes is more likely to be present in recurring attacks of pancreatitis and is a feature of the advanced stage of chronic pancreatitis

PATHOGENESIS OF PANCREATITIS

Though the aetiological factors responsible for *pancreatitis are frequently* well defined there is as yet no common agreement on the fundamental mechanism which *initiates the on et of the disease Even in the more severe types with necrosis* about which much has been written there are conflicting views Few new facts have been acquired since the reviews of *McWhorter (1932) Dragstedt Haymond* and Ellis (1934) Rich and Duff (1936) Lewison (1940) and the admirable essay in which Jones (1943) discussed the available data and current views *held at that time* In the last few years however a more comprehensive conception of the mechanism responsible for attacks of pancreatitis has been developed

Pancreatitis is an autolytic process non infective in character The factor common to all cases is the release of activated enzymes into the interstitial tissue of the pancreas Of these the lipolytic and proteolytic enzymes are the more important Bacterial infection does not play a part in the inception of the disease process though later infection of necrotic tissue may lead to suppuration Conclusive proof of the means by which the enzymes are activated has not yet been obtained *and there is no* certainty whether this conversion takes place before or after the release of the enzymes into the tissues

Experimentally pancreatitis can be caused by the injection of any of a large variety of substances including bile into the pancreatic duct either following or without ligature of the *major ducts The pancreatitis* which is produced by these injections has been regarded as due to activation of trypsinogen within the ducts Since however *the volume of the injections is usually* considerable the effects of such procedures might equally be brought about by the rupture of the

finer ducts and acini releasing enzymes into the tissues (Rich and Duff 1936) Pancreatitis does not follow ligature of the ducts alone but does occur when in addition to ligation the gland is actively stimulated to secrete The rise in pressure in the duct system and rupture of the acini is followed by the absorption of enzymes into the blood stream and a consequent increase in the level of serum amylase and lipase In man an obstruction of the pancreatic duct is sometimes met and is associated with varying d grees of activity of pancreatitis for instance in carcinoma of the duct in pressure from a duodenal diverticulum or when roundworms lodge in the pancreatic duct Clinical pancreatitis sometimes develops a few hours after a heavy m al associated with alcohol when pancreatic secretion is at its height The concentration of enzymes in the juice at that time is po sibly a factor which determines the onset and severity of the reaction On the other hand in the late stages of chronic pancreatitis when acinar function is destroyed painful episodes cease

In rupture of the pancreas due to blunt trauma or when vascular accidents impair the local nutrition of the gland enzym s are released locally which may cause pancreatitis In these circumstances it is not nec ssary to postulate an intraductal activation of enzymes nor yet in the local pancreatitis of more chronic type associated with penetrating ulcer of the duod num The other possibility that activation occurs in the acinar and interstitial tissues must be considered In mild cases of acute pancreatitis oedema of the gland exists In most though not all of these some local fat necrosis can b seen The lesions due to the liberation of trypsin are not invariably seen which is contrary to what would be expected if activation of this enzym in the duct syst m was a necessary antecedent to the development of pancreatitis The activation of trypsinogen in the interstitial tissues of the pancreas may well be related to the products of tissue reaction of fat digestion brought about by lipase Calcium salts or a pH approaching neutrality are known to be factors in initiating the conversion of the inactive to the active enzyme and trypsin its lf once the conversion has b gun is capable of activating more trypsinogen In this respect the greater the con centration of the enzyme the greater its potentiality for self activation

Any consideration of the causal factors in pancreatitis must recognize the as ociation with biliary tract disease in roughly 50 per c nt of cases For 50 y ars since Opie (1901) reported on Halsted s (1901) fatal case of acute pancreatic necrosis the common channel theory has been most popular In that case a small stone lodged in the sphincter at the duodenum converted the two ducts which joined some millimetres proximally into a common channel Opie noted bile staining in the pancreatic duct but as Rich and Duff (1936) point out it is perhaps significant that he followed the usual practice of morbid anatomists and had earlier squeezed the gall bladder to ascertain the patency of the common duct and did in fact with difficulty obtain a few drops of bile at the duodenal orifice Opie concluded from his experiments in which he injected bile into the pancreatic duct that reflux of bile was an aetiological factor It is doubtful however if the pressure in the biliary tract even with a healthy gall bladder would be sufficiently great to cause reflux of bile It has been stated that the secretory pressure of the pancreas equals or exceeds that of the liver (Herring and Simpson 1909 Mann and Giordano 1923 Harms 1927) though Dragstedt Haymond and Ellis (1934)

consider that the effective pressure in the pancreatic duct would be lowered in cases where a free anastomosis of the major pancreatic ducts exists It is not known however in what proportion of cases of acute pancreatitis a common channel is found or if a free anastomosis of the duct of Wirsung with the duct of Santorini is present in all cases of pancreatitis Anatomical studies on normal individuals do not elucidate this problem

Another explanation can be given of the finding of bile in the pancreatic duct at operation or autopsy When a common channel is formed the rise in pressure in the biliary and pancreatic systems ruptures the more fragile ductules of the pancreas more readily than the bile canaliculi and consequently pressure falls in the pancreatic duct Herring and Simpson (1909) observed a similar fall of pressure in their experiments and proved it to be due to widespread extravasation of pancreatic juice into the tissues It is conceivable that in these circumstances bile may flow into the pancreatic duct The presence of bile in the duct is not however an essential feature of the production of pancreatitis There is some evidence which points to a flow of pancreatic juice in the reverse direction into the biliary system (Colp and Doubilet 1938) Popper (1942) found pancreatic enzymes in the bile in 11 out of a series of 18 cases of acute pancreatitis Indeed attempts have been made to attribute gall bladder disease to the presence of trypsin in that organ (Wolfer 1931 1937)

A stone is found blocking the sphincter in the way described by Opie in a small proportion of cases and can be a factor producing pancreatitis in only a few patients Archibald (1919) suggested that spasm of the sphincter muscle would explain those cases in which no stone is found at the ampulla but stones are present elsewhere in the biliary tract and particularly in the gall bladder neck That such spasm can occur is verified by pressure and cholangiographic studies made by numerous workers (McGowan and others 1936 Doubilet and Colp 1937) and spasm can be accepted as a cause of increase in intraductal pressure

Metaplasia of the duct epithelium postulated by Rich and Duff as a cause of obstruction to the pancreatic ducts is not now considered of importance as a primary aetiological factor It seems more likely that this is a phenomenon secondary to pancreatitis and the argument of these authors on this matter which is based on misconceptions of the true nature of cystic fibrosis of the pancreas and vitamin A deficiency can in the light of present knowledge no longer be accepted

Summary —It seems likely that the factors producing pancreatitis act through a single mechanism the release of enzymes into the interstitial tissues of the pancreas This in turn is due (with some exceptions such as trauma in mumps in penetrating ulcers and in vascular accidents) to obstruction of the duct of an actively secreting gland This hypothesis accounts for the known experimental and clinical facts and has been of practical value in providing a rational basis for the management of both the acute and chronic forms of pancreatitis

NATURAL HISTORY OF PANCREATITIS

Pancreatitis is more common than was believed 10 years ago An increasing awareness of the role played by the pancreas in producing upper abdominal symptoms and improved methods of confirming the diagnosis have led to the

detection of earlier and milder forms The recognition of a milder type of acute pancreatitis followed the development and use of more accurate methods of measuring serum amylase It is largely due to the writing of Elman that this form has been more widely appreciated Elman (1933) called this condition acute interstitial pancreatitis to differentiate it from acute haemorrhagic necrosis The course of the former is relatively benign and the mortality is low in the latter the mortality is high

Though the complete identity of these two conditions has not been proved it seems reasonable to accept that they are essentially the same process differing only in their severity In mild cases the lesion may heal and leave no scar On the other hand structural derangements may remain and the recurring episodes of pancreatitis which follow may lead finally to a grossly atrophic gland incapable of function For such cases Comfort and his colleagues from the Mayo clinic have revived an old name of chronic relapsing pancreatitis in their classical and illuminating papers (1946 1947) They have emphasized that there is a tendency to exacerbation and remission associated with a progressive destruction of the gland until a final stage of chronic pancreatitis may be reached On the other hand several attacks of pancreatic oedema may leave no trace of structural defect in the gland and there may be complete restoration of function For these cases the more appropriate name of acute relapsing pancreatitis is used

The clinician gain much by accepting the unified pathological conception of pancreatitis put forward by Comfort at least in our present state of knowledge There is no essential difference in the various types of pancreatitis but the eventual outcome is the sum of the extent and severity of the destructive process in the gland and the reparative reaction of the body to this destruction At least in the more advanced cases the anatomical picture seen at operation and on biopsy is mirrored by changes in function which can be estimated There is however considerable functional reserve in the pancreas and early changes may lead to no measurable functional defect This is particularly true of the quiescent phases of the disease It is hoped that by improving functional tests an earlier diagnosis may permit of earlier treatment and prevention of the later episodes

Pathologically pancreatitis can be classified as follows

Acute phase—(*a*) Acute interstitial pancreatitis (1) oedema of the pancreas (2) oedema of the pancreas with local fat necrosis (*b*) acute haemorrhagic necrosis of the pancreas (1) acute haemorrhagic pancreatitis (2) acute necrotic or gangrenous pancreatitis and (3) acute suppurative pancreatitis

Relapsing phase—(*a*) Acute relapsing pancreatitis (*b*) chronic relapsing pancreatitis

Final phase—Chronic pancreatitis (1) localized (2) diffuse (3) with pancreatic lithiasis and (4) with calcification of the pancreas

Acute pancreatitis

Local effects—The release of enzymes into the interstitial tissues of the pancreas is followed in the early stages by swelling and oedema The induration affects particularly the head of the gland At operation some brownish fluid may be found in the lesser sac the gland on inspection is whiter than normal and tiny

areas of fat necrosis can be seen. There is cellular infiltration into the interstitial tissue. Usually this stage subsides spontaneously but in more severe cases the process spreads into the peripancreatic tissues of the upper abdomen and more extensive areas of fat necrosis are seen in and around the pancreas.

It may be, as has been said, that the products of fat hydrolysis are necessary for the initiation of the activation of trypsinogen. The release of the trypsin is followed by signs of widespread proteolytic and necrotizing reaction well described by Rich and Duff (1936). They claim with convincing experimental support that the vascular lesions caused by trypsin digestion are responsible for the developing pathological picture. The haemorrhages and thrombosis of the vessels which follow this release may impair the nutrition of large areas of the pancreas and lead to necrosis, gangrene and sloughing. At this stage the field is open to secondary invasion of sloughs by bacteria and suppuration and abscess formation may ensue. A spreading peritonitis may result from the release of blood and enzymes in the abdomen, or from the bacterial invasion of secretions and devitalized tissues. Doubilet and Mulholland (1949) have drawn attention to a more local peritonitis which may follow the outpouring of fluid from the lesser sac causing a pericholecystitis with adhesions of omentum, transverse colon, pylorus and duodenum to the under surface of the liver. Spread may also occur into the peritoneal cavity. This leads to the localized ileus of the transverse colon or upper jejunal loops which is sometimes seen in acute pancreatitis. Jaundice is not an infrequent finding in severer forms and is due either to stone in the common bile duct or, more usually, to occlusion of the duct by the inflammation in the head of the gland. Haematemesis may rarely complicate the picture and the enlargement of the spleen occasionally found after an attack is probably due to splenic vein thrombosis.

During resolution local abscesses may occur in the abdomen and subphrenic collections of fluid may be present. Retention cysts are found in the pancreas when secretions empty into necrotic areas and a pseudocyst of the lesser sac may form when the foramen of Winslow has been sealed off by the inflammatory reaction. (These pseudocysts are particularly prevalent after blunt trauma to the abdomen but may also develop after an acute attack of diffuse pancreatitis.) Their presence may be overlooked till several weeks or months after the acute episode when an enlarging tumour in the upper abdomen becomes obvious.

General effects.—The release of amylase and lipase into the interstitial tissues leads to their direct absorption into the blood stream as shown by elevation of the serum amylase and lipase values and a rise in excretion of amylase in the urine. This rise occurs only so long as the gland is functioning. Peripheral fat necroses have been observed in the perinephric fat and in the limbs (Blauvelt, 1946). This is presumably due to the release of lipase at these sites. Fat necrosis has also been seen in the mediastinum, but here the transfer may be made by the lymphatic system. In spite of an anti-trypsin in blood serum, liberated trypsin may at least partly account for the blotchy, cyanotic discolorations and haemorrhagic lesions which have been described on the trunk and thighs in some cases of pancreatic necrosis.

Upset of the electrolyte balance may be an important feature of the disease. Changes occur in the electrocardiogram of a non-specific type with inversion of

T waves and depression of the S-T segments (Gottesman Casten and Beller 1943) The Q-T interval may be prolonged and a U wave may appear These have been attributed to lowered potassium in the serum (Bockus and Raffensperger 1948) and should not be confused with changes which occur in acute myocardial infarction due to coronary occlusion A fall in serum calcium occurs from the third to eleventh days in the severer grade of acute pancreatitis (Edmondson and Fields 1942 Edmondson and Berne 1944) This is attributed to the mobilization of calcium to combine with the fatty acid released in the upper abdomen by lipolysis Large amounts of calcium are present in this region at autopsy A fall in serum calcium however should not be taken as a diagnostic criterion it is more important as a gauge of severity of the process It is not at the moment clear why calcium is not mobilized from body reserves to compensate for the fall in blood calcium

The inflammatory process may be so severe and widespread that the endocrine function of the pancreas may be affected Transient glycosuria or hyperglycaemia may be found in the acute phase and a glucose tolerance test performed in the recovery period reveals a disturbance of insulin production more frequently than is generally believed In less severe cases and in first attacks the endocrine function may return to normal over a period of weeks or months but in some cases particularly of the relapsing type the impairment becomes a permanent feature

Chronic pancreatitis

Chronic recurring pancreatitis (Comfort Gambill and Baggenstoss 1946 Gambill Comfort and Baggenstoss 1948)

Recurring attacks of pancreatitis are not uncommon In some cases a single episode may be followed by resolution or some degree of interstitial fibrosis In others recurring attacks with varying severity of interstitial fibrosis and residual necrosis may lead to progressive destruction of the gland Regions of diffuse calcification in the gland or upper abdomen pseudocysts and abscesses are less common sequels In a few cases calculi may form in the duct system

The acute phases which may recur after long or short intervals of clinical quiescence are manifested by painful crises in the upper part of the abdomen and by disturbances of acinar and islet cell function At first these disturbances are transitory during the quiescent phases though there may be little evidence of functional derangement yet the gland may show pathological changes Later in the course of the disease however the destruction of the pancreas reaches a point where glycosuria and hyperglycaemia persist and the stools are fatty and contain excess nitrogen At this stage pancreatic calcification may be seen occasionally on skiagrams Enlargement of the pancreas may lead to obstruction of the common bile duct with consequent jaundice distension of the gall bladder and liver cell damage

Terminal phase—chronic pancreatitis

Finally the fully developed syndrome of chronic pancreatitis develops with diabetes steatorrhoea and creatorrhoea Loss of weight from deficient absorption food intolerance asthenia and incapacity for work are physical features of this malady to which must be added the psychological disturbances associated

with a long and painful affliction The sufferers turn to alcohol or morphine for solace In a few cases the relief of pain is the major problem presented to the physician

DIAGNOSIS OF PANCREATIC DISEASE

The diagnosis of pancreatitis consists essentially of suspecting that a lesion of the pancreas might account for the patient s symptoms and attempting to add proof to the suspicion by using the appropriate pancreatic function tests The words of Garrod (1920) when discussing this subject still hold true today The more constantly we bear the pancreas in mind as a possible seat of origin of obscure abdominal troubles the less likely shall we be to overlook its lesions Even to the clinician who is aware of the possibility of acute pancreatitis confusion arises with other acute abdominal conditions perforation of a peptic ulcer intestinal obstruction mesenteric thrombosis and particularly acute cholecystitis Cardiac infarction when the pain is referred to the abdomen and dissecting aortic aneurysm may mimic acute pancreatitis clinically

An analysis of the site localization and reference of the pain which is the most highly developed of our methods of clinical study in abdominal disease frequently fails to differentiate between these various upper abdominal lesions Chapman Herrera and Jones (1949) have pointed out the striking similarity of pain induced by experimental stimulation of the common bile duct and upper small intestine on the one hand and the pain of biliary tract disease and pancreatitis on the other This they attribute to the common afferent nerve supply mediated by the greater splanchnic and lower thoracic sympathetic nerves

Two other recent studies of pancreatic pain have been made one experimental the other clinical Bliss Burch Martin and Zollinger (1950) determined the pattern of pain elicited by electrical stimulation of the head body and tail of the pancreas in patients who had undergone operations on the biliary tract Pain arising in the head of the pancreas is referred to the right of the mid line from the xiphoid to just below the umbilicus in the body to the same areas but now in the mid line in the tail to the left of the mid line from the xiphoid down to just above the groin Radiation of the pain may occur through to the back on the same side With maximal stimulation or on stimulating all three areas a band like pain is felt across the abdomen above the umbilicus and passing through to the back

Clinically in diffuse pancreatitis the primary site of the pain may be in the right middle or left part of the epigastrium or rarely in the lower thoracic region of the back (Comfort Gambill and Baggenstoss 1946 Gambill Comfort and Baggenstoss 1948) From the primary site pain may radiate to various parts of the abdomen left anterior thorax but most often to the thoraco lumbar area of the back Pain starting in or shifting to the left upper abdomen the left side of the back or to the left shoulder tip is most characteristic of pancreatitis (Gambill 1947) It will be appreciated however how easily confusion can occur particularly with acute cholecystitis and when peritonitis follows acute pan creatitis how difficult it may be to differentiate the condition from perforation or other acute abdominal emergencies which result in peritonitis

Certain features of the pain other than localization may be important The onset of pain is usually sudden and takes place at the height of digestion \ frequently after a heavy meal or alcohol If the pain starts more gradually it rapidly increases till a plateau of severity is reached which lasts for a period of a few hours or days and thereafter gradually subsides (Gambill 1947) The attacks seldom last less than two days, according to Comfort (1947) and the long duration of the attack is considered to be the characteristic feature which dis tinguishes the pain of pancreatitis from that of biliary colic In addition the pain of pancreatitis tends to be sustained rather then colicky though waves of accentu ation may be superimposed upon the steady pain which is variously described as burning sharp stabbing pressing or aching (Gambill 1947) The patient may obtain some ease on flexing the trunk The pain is often so severe that frequent hypodermic injections of morphine are required to give relief Milder attacks however are being more frequently recognized indeed pain may not be an invariable feature for elevated values of serum amylase do not always coincide with a painful episode When the pain is mild the attack is usually of shorter duration In these cases the history of previous episodes of upper abdominal distress which have been recognized as due to pancreatitis helps the physician to appreciate the significance of the symptoms

Acute pancreatitis

Other symptoms and signs are often no more informative than is an analysis of the pain in the differential diagnosis of acute pancreatitis The most suggestive signs are rigidity and guarding in the left upper abdomen tenderness in the epigastrium and left loin the state of shock the peculiar cyanosis and the onset of jaundice The bluish discoloration of the flanks and slate blue colour of the umbilicus (Grey Turner s sign 1920) are unusual events It is fortunate that in the serum amylase we have a test of sufficient specificity to be of the greatest value To obtain the best results serum should be taken early in the illness In mild cases the rise is evanescent and may be gone in 48 hours In severe attacks destruction of the pancreas may prevent the secretion of enzymes in the late stages Most information can be gained from the test when repeated estimations are made during the first few days If the case is seen after the first few days urinary amylase or serum lipase values may be raised after the serum amylase has returned to normal Other ancillary tests of value early in the acute stage are the leucocytosis which occurs in the more severe grades and a plain film of the abdomen in the erect position may reveal localized ileus This finding is not pathognomonic of acute pancreatitis but when present usually affects the trans verse colon but also occurs in the upper jejunum or even the stomach Glycosuria or hyperglycaemia during the acute attack favours the diagnosis of pancreatitis

Quiescent phase

When the patient is seen after the acute attack has passed a diagnosis in retrospect may be difficult Milder attacks may quickly settle and leave no trace in the gland and no functional impairment However in more severe cases localized collections of fluid in the lesser sac or pseudocysts may be palpable as a tumour in the upper abdomen Calcium deposits may be seen in this cystic area on abdominal skiagrams

and barium studies of the stomach duodenum *and colon may reveal the* displacement of these viscera Adhesions in the region of the duodenum may lead to a deformity of the duodenal cap which should *not be mistaken for the* deformity of duodenal ulcer (Doubilet and Mulholland 1949) In the early stage after pancreatitis the gall bladder may not fill with *opaque dye but a* satisfactory shadow may be present some months later Shortly after the acute phase the output of bicarbonate and amylase in the duodenal contents *in response* to secretin may be diminished At this stage too up to 8–12 weeks after an attack stimulation with secretin may elevate the serum enzymes If hyperglycaemia has been a feature of the acute phase some improvement in the diabetic condition can be anticipated and this is of diagnostic value It must be admitted however that frequently the diagnosis remains in doubt at this stage and the true nature of the lesion may be revealed only when a second attack follows

Chronic pancreatitis

Radiological examination may reveal calcification in the gland or in the upper abdomen Not infrequently such deposits are overlooked or attributed to some other cause such as tuberculous mesenteric glands In the advanced stages established diabetes is common and defects of external secretion are manifest The secretin test shows that the volume of the duodenal contents obtained is low as is the bicarbonate output All enzyme values may be markedly depressed and *no elevation in serum enzymes will occur following stimulation of the gland as* acinar function deteriorates The stools may be fatty and greasy and contain undigested *muscle fibres and neutral fat Fat balance studies may show an* excretion in the stools of an excess of 10 per cent of the fat intake and more than 2 5 grams *of nitrogen may appear daily in the stools*

In the later phases of chronic relapsing pancreatitis where several episodes of pain have *occurred the diagnosis* becomes much more certain At this stage calcification and advanced defects of external or internal secretin become prominent *features* and the demonstration of more than one of these anomalies in the presence of the characteristic upper abdominal crises is conclusive evidence of an advanced stage of chronic pancreatitis

Summary —When the patient is seen in either the acute or chronic phase of pancreatitis the diagnosis is usually possible if full use is made of the available diagnostic procedures It is in the inactive and quiescent phase that the diagnosis is difficult At this stage the suspicion of pancreatic disease may only arise when investigations have failed to disclose a cause of upper abdominal *symptoms such* as peptic ulcer or gall bladder disease It must be remembered however that pancreatitis may exist as a concomitant lesion in the presence *of gall stones and* all means hould be sought to confirm a suspicion of pancreatitis for it is in the early treatment of biliary *disease that prophylactic surgery finds its greatest use*

TREATMENT

The acute attack

The controversy between the protagonists of conservative and operative treatment in acute pancreatitis has been carried on for some time The balance of opinion *now favours* the less radical approach to the problem especially in the milder

cases In pancreatic necrosis however there is still a body of influential surgical opinion in favour of early operation The gathering of comparable statistics on this subject is difficult for necrosis is not common and a series of cases submitted to operation in the past is not truly comparable with a present day eries when the diagnosis of milder cases is much improved Even though cases of graded severity are compared it is difficult to arrive at an accurate assessment of the influence of immediate operation on the mortality rate

In animal experiments it has long been known that handling the pancreas at operation in acute pancreatitis has had a detrimental effect, and there is little in favour of an emergency operation when the diagnosis is certain Even when the diagnosis is in doubt there are few abdominal emergencies in which the patient will not benefit from restorative treatment while a serum amylase is being estimated This procedure can be completed in an hour and should be within the capacity of resident clinical pathologists The raised value early in the course of an abdominal crisis is fortunately highly specific and is indeed often essential to confirm a diagnosis of pancreatitis If by chance the abdomen has been opened and acute pancreatitis is found the handling of tissues in the upper abdomen should be avoided It is unlikely that drainage of the biliary tract will necessarily relieve pressure in the pancreatic duct after pancreatitis has developed Once the condition is recognized even drainage of the lesser sac is inadvisable for from experimental and clinical data it is suggested that anaesthesia alone may be harmful and increase the mortality in severer cases If operation is decided upon the optimum time is at a later stage when the induration of the gland has subsided or the inflammatory lesion has localized

The conservative management of an acute attack of pancreatitis is based on the following principles

1 *Relief of pain*

Repeated hypodermic injections (Injectio Morphinae Sulphatis *B P* $\frac{1}{6}$–$\frac{1}{3}$ grain or 10–20 milligrams) may be required to relieve the pain of a severe attack Morphine alone is inadvisable in the treatment of the acute attack as it is in acute biliary disease because it causes spasm of the sphincter of Oddi It is however often necessary for there is as yet no satisfactory substitute It was thought that pethidine (Injectio Pethidinae Hydrochlor *B P* 100 milligrams intramuscularly which may be repeated in from one to three hours) would be the drug of choice because of its mild anti vagal action Gaensler McGowan and Henderson (1948) have reported that biliary pressure is increased by pethidine presumably from spasm of the sphincter of Oddi Though these authors thought it caused almost as much spasm as morphine Utendorfer and Bergh (1948) found that no spasm resulted from the parenteral injection of 50 milligrams but spasm followed when 100 milligrams were given The spasm produced by these drugs is relieved by nitrites aminophylline and adrenaline but not by atrophine and papaverine Glyceryl trinitrate is a satisfactory drug to use with morphine and pethidine (Tabella Glycerylis Trinitratis $\frac{1}{60}$ grain or 1 milligram two tablets are chewed and dissolved under the tongue) It acts in 2–3 minutes the effect lasting some 30 minutes but the dose may be repeated frequently for it is not a cumulative drug Apart from its combination with morphine this drug may usefully be given

alone to abolish sphincter spasm early in an attack of acute pancreatitis (Elman 1939) before induration of the head of the pancreas produces mechanical obstruction of the pancreatic and common bile ducts

A block of the paravertebral sympathetic nerve fibres carrying the pain afferents from the pancreas has been recommended in the acute phase for the relief of pain The disadvantage of this procedure and of the use of the ganglion blocking drugs tetraethylammonium bromide and chloride is that they may inhibit the splanchnic constriction which reduces the external secretion following acute pancreatic lesions On the other hand some writers believe that vascular spasm may be a factor aggravating pancreatitis The fall in blood pressure following these drugs would also be undesirable in severe cases with shock In the acute attacks of pain which accompany the later stages of chronic relapsing pancreatitis when pancreatic function is largely destroyed there is more to be said in favour of sympathetic block

Rest to the pancreas

Vagal inhibition —This is best achieved by giving atrophine sulphate (1/60 grain or 1 milligram and repeating 1/100 grain or 0 6 milligram 4 hourly) The drug is given to the limit of tolerance This will depress direct vagal action on the pancreas and influence the pancreas indirectly by reducing the volume of gastric secretion There is no advantage in prescribing the atrophine like drugs trasentin and syntropan

Hormonal inhibition —Food is withheld by mouth and all nourishment is given by the parenteral route until decided improvement occurs A gastric suction tube is passed and every effort is made by constant suction to prevent the escape of gastric secretion into the duodenum The tube requires continual attention and is probably the most important single therapeutic weapon in dealing with the disease process If the desired result is obtained release of secretin and pancreozymin is probably negligible

Relief of dehydration and electrolyte imbalance

Fluid and electrolyte balance should be ensured along the usual lines In the stage of shock blood transfusions are indicated Plasma infusion carries too great a risk of subsequent hepatitis to be recommended When glucose is given frequent estimations of blood sugar should be made to guard against excessive hyperglycaemia and insulin is given as indicated The influence of hyperglycaemia and hypoglycaemia on the pancreatic secretion in man is at present uncertain It is certain however that both extremes are deleterious to the patient It should not be forgotten that the serum calcium and potassium may fall short of normal levels There are few conditions in which the resources of a reliable biochemical laboratory can be so valuable in the hour by hour management of a seriously ill patient as pancreatic necrosis In severe cases when intravenous alimentation is necessary for longer than 48 hours the intravenous administration of amino acids helps to maintain nitrogen balance

Prevention of infection

Penicillin or preferably streptomycin is given in adequate dosage to prevent secondary bacterial invasion of the affected area

Choice of time for operation

It is better after an attack of acute pancreatitis to postpone operation till the inflammatory reaction in the upper abdomen resolves or localizes This of course may not always be possible Spreading peritonitis an epigastric mass due to cyst or abscess formation or some other complication may necessitate earlier operation Again in some mild cases there may be no indication for operation at all But the primary factor responsible for pancreatitis in 50–60 per cent of cases proves to be a lesion of the biliary tract and preventive surgery should be undertaken to eradicate the fundamental cause of the pancreatitis as well as therapeutic surgery to deal with inflammatory residues in the abdomen Unfortunately radiological examination of the gall bladder is usually not of value in deciding the need for operation for the gall bladder may fail to fill with opaque dye for several weeks after pancreatitis

Doubilet and Mulholland (1949) suggest that the best time to explore the upper abdomen is the third week after onset of the acute condition By this time the induration of the head of the pancreas will be settling and if operation is indicated the delay should not be so long that further attacks can take place The diseased gall bladder and gall stones in the common duct should be removed The common duct should be thoroughly explored and T tube drainage employed (Waugh 1947) Cholangiograms are being made with increasing frequency following this operation on the biliary tract Attempts have also been made to deal with the sphincter spasm at the lower end of the common duct Doubilet and Mulholland have reported good results from splitting the sphincter muscle An adequate appraisal of the method can only be made after a long term review of patients on whom this manoeuvre has been employed Certainly other attempts to deal with this spasm for instance by a local denervation of the sphincter seem to have proved valueless in biliary dyskinesia (Lagerlöf 1947)

Treatment of chronic relapsing pancreatitis

The results of conservative surgical procedures are sufficiently good to justify their use in the first instance (Comfort Gambill and Baggenstoss 1946) The earlier in the course of the disease surgical treatment is carried out the more likely will con ervative measures prove adequate (Waugh 1947) Indications for treatment by surgery are duodenal obstruction common bile duct obstruction and the presence of pancreatic tumour due to cyst or abscess Anastomosis of the common bile duct or gall bladder to the jejunum is often necessary Calculi obstructing the larger pancreatic ducts have been successfully removed (Lionelli Ficarra and Ryan 1944) The indications for sphincterotomy apply equally to this group of cases and the encouraging results reported justify a further trial of this method (Doubilet and Mulholland 1950) Richman and Colp (1950) have described subtotal gastrectomy with vagotomy as an operation to reduce pancreatic secretion in chronic relapsing cases and Chisholm and Siebie (1947) have suggested that small doses of x rays might achieve the same object

Between acute exacerbations of pancreatitis treatment is largely symptomatic Alcohol is forbidden The nutrition of the patients should be improved with a bland diet containing adequate protein and vitamins Protein and vitamin supplements are useful Fat is curtailed and indeed the patient is frequently

intolerant of fat An alkaline powder is given after meals which should be small Aluminium hydroxide which interferes with the absorption of phosphate in pancreatic insufficiency is not a suitable antacid (Fauley and others 1941) Interval feeds are given to raise the calorie intake Diarrhoea is improved by the fat restriction and in more advanced cases the value in this respect of substitution therapy consisting of adequate amounts of an active pancreatin preparation (up to 24 grams daily) has been proved by Beazell Schmidt and Ivy (1941) The use of emulsifying agents of the type of polyoxyethylene sorbitan mono oleate (Tween 80) in an effort to increase the absorption of neutral fat is worth a trial (Jones Culver Drummey and Ryan 1948) Deficiency of internal secretion should also be countered by the administration of insulin Fatty livers are not seen in patients to whom adequate protein is given

Relief of pain

It must be admitted that in some cases of chronic relapsing pancreatitis with painful seizures the relief of pain is the major problem set the physician The disability and invalidism associated with persisting bouts of pain are so severe that quite often the patient turns to alcohol or morphine for relief When other conservative measures have failed Comfort and others (1946) and Whipple (1946) thought a partial or total pancreatectomy justified Such operations are however technically difficult on account of previous peripancreatitis and the mortality is forbidding In these circumstances unilateral or if necessary bilateral splanchnicectomy with removal of the thoracic sympathetic chain from the sixth thoracic to the first lumbar ganglia an operation first performed by the French surgeons has given sufficiently good short term results in the hands of several workers that its use can be recommended A block of the sympathetic afferents is a useful preliminary to the major operation (Malet Guy Jeanjean and Servettaz 1945 Marion 1945 de Takats and Walter 1947 Ray and Console 1949 Conolly and Richards 1950 de Takats Walter and Lasner 1950)

MODERN TRENDS OF OPINION ON PANCREATITIS

In acute pancreatitis the earlier treatment is instituted the more favourable is the response The outlook becomes graver if the activity of the process is not controlled before induration of the head of the pancreas causes mechanical obstruction of the pancreatic duct and leads to irreversible changes in the gland In recurring pancreatitis also when the aetiological factors which predispose to further attacks and disorganization of the pancreas are dealt with early in the course of the disease the chances of cure are increased

Since early diagnosis is important it is unfortunate that the diagnosis of pancreatitis on clinical grounds is frequently difficult and often impossible A review of the reports by different workers shows that an accurate diagnosis of acute pancreatic necrosis before operation is rarely made and at best does not exceed 40 per cent This percentage would probably be raised considerably if more extensive use were made of serial determinations of serum amylase and lipase during attacks of acute upper abdominal pain These tests should be used also in other less severe attacks of upper abdominal discomfort the causes of

which are uncertain The surgeon when he performs an operation on the upper abdomen should be prepared to inspect palpate and assess the condition of the head body and tail of the pancreas Though the association of pancreatitis with gall stones is well known the frequency with which this complication occurs is probably not fully appreciated and in the presence of biliary tract disease search should be made to exonerate the pancreas of suspicion of disease

Since these measures taken during the acute stages would increase the number of cases of pancreatitis recognized the physician mindful of the possibility of pancreatic disease should make every effort to confirm the diagnosis during the acute attack As time passes following the acute attack the diagnosis becomes more and more difficult to establish unless permanent damage of the gland develops Tests which involve the recovery of duodenal enzymes and estimations of serum enzymes following stimulation of the pancreas may for some weeks after the acute attacks still show impairment of pancreatic function but these tests are tedious and are not as yet sensitive enough for great reliance to be placed on negative findings Some time after the acute attack at most 3 months when the pathological process in the gland subsides complete function may be restored and tests of pancreatic function become of less value

The present trend in the study of the diagnosis of pancreatitis is to develop pancreatic function tests which are sufficiently sensitive to reveal functional disorders of the pancreas at an early stage and to indicate the individual who has a diseased pancreas It appears likely if full use is made of the recent physiological advances in our knowledge of the pancreas that such functional tests will be developed It is hoped that they may achieve the same degree of usefulness which is attained by modern tests of hepatic function As yet however there is no uniformity in method technique or interpretation of many pancreatic function tests The optimum dosage of stimulant material which appears to be necessary to give more exact information has not yet been decided It is not yet known how far impairment of function reflects the pathological changes present in the gland at the time of the test Until this is known function tests cannot be interpreted too strictly in terms of pathological changes Nevertheless at present the functional aspects of pancreatitis which have been discussed in this chapter appear to be the most fruitful and promising approach to the study of pancreatitis

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REFERENCES

Ågren G and Lagerlof H (1936) *Acta med scand* 90 1
— — (1937) *Ibid* 92 359
Allan F N Bowie D J Macleod J J R and Robinson W (1924) *Brit J exp Path* 5 75
Anrep G V (1916) *J Physiol* 50 421
Archibald F (1919) *Surg Gynec Obstet* 28 529

Babkin B P (1950) *Secretory mechanism of the digestive glands* 2nd ed New York and London Hoeber
Banting F G and Best C H (1922) *J Lab clin Med* 7 251
Baxter S G (1931) *Amer J Physiol* 96 349
Bayliss W M and Starling E H (1902) *J Physiol* 28 325
Beazell J M Schmidt C R and Ivy A C (1941) *J Amer med Ass* 116 2735
Bernard, C (1849) *Du suc pancréatique et de son role dans les phénomènes de la digestion* Paris Rignoux
— (1856) *Leçons de Physiologie experimentale* Vol 2 p 170 Paris Baillière
Best C H (1948) *Diabetes and insulin and the lipotropic factors* Springfield Ill Thomas
Black D A K Bound J P and Fourman L P R (1947) *Quart J Med* 16 99
Blauvelt, H (1946) *Brit J Surg* 34 207
Bliss W R Burch B Martin M M and Zollinger R M (1950) *Gastroenterology* 16 317
Bockus H L (1946) *Gastro enterology* Vol 3 Philadelphia and London Saunders
— and Raffensperger E G (1948) *N Y St J Med* 48 2252
Bolgert M (1935) *Lésions du pancréas et troubles fonctionelles pancréatiques* Paris Masson
Burke J O Plummer K and Bradford S (1950) *Gastroenterology* 15 669
Chaikoff I L and Entenman C (1948) *Advances in Enzymology* Vol 8 p 171 New York Interscience
Chapman W P Herrera R and Jones C M (1949) *Surg Gynec Obstet* 89 573
Cherry I S and Crandall L A (1932) *Amer J Physiol* 100 266
Chiray M Salmon A R and Mercier A (1926) *Bull Soc méd Hop Paris* 50 1417
— Jeandel A and Salmon A (1930) *Pr med* 38 977
— Bardet N and Taschner E (1931) *Arch Mal Appar dig* 21 1137
Chisholm T C and Siebie R E (1947) *Surg Gynec Obstet* 85 794
Colp R and Doubilet H (1938) *Ann Surg* 108 243
Comfort M W and Osterberg A E (1940a) *Arch intern Med* 66 688
— — (1940b) *Proc Mayo Clin* 15 427
— — (1941) *Amer J digest Dis* 8 337
— Gambill E E and Baggenstoss A H (1946) *Gastroenterology* 6 239 376
— (1947) *Proc Mayo Clin* 22 548
— Dornberger G R Wollager E E and Power M H (1949) *Gastroenterology* 13 135
Conolly J E and Richards V (1950) *Ann Surg* 131 58
Cooke W T Elkes J J Frazer A C Parkes J Peeney A L P Sammons H G and Thomas G (1946) *Quart J Med* 15 141
Crittenden P J and Ivy A C (1937) *Amer J Physiol* 119 724
Diamond I S Siegel S A Gill M B and Karlen S (1939) *Amer J digest Dis* 6 366
— — and Myerson S (1940a) *Rev Gastroenterol* 7 429
— — — (1940b) *Amer J digest Dis* 7 133
— — (1940) *Ibid* 7 435
— — (1941) *N Y St J Med* 41 869
Dolinski I L (1894) Quoted by Pavlov I P (1902)
Dornberger G R Comfort M W Wollager E E and Power M H (1948a) *Gastro enterology* 11 691
— — — — (1948b) *Ibid* 11 701
Doubilet H and Colp R (1937) *Surg Gynec Obstet* 64 622
— and Mulholland J H (1949) *Surg Clin N Amer* 29 339
— — (1950) *Ann Surg* 132 786
Dragstedt L R Haymond H E and Ellis J C (1934) *Arch Surg Chicago* 28 232
— Prohaska J V and Harms J P (1936) *Amer J Physiol* 117 175
— Vermeulen C Goodpasture W C Donovan P B and Geer W A (1939) *Arch intern Med* 64 1017
Dreiling D A and Hollander F (1948) *Gastroenterology* 11 714
— (1950) *Ibid* 16 162
— and Hollander F (1950) *Ibid* 15 620
Duncan P R Harper A A Howat H T Oleesky S and Varley H (1950) *J Physiol* 111 63P
Edmondson H A and Fields I A (1942) *Arch intern Med* 69 177

Edmondson H A and Berne C J (1944) *Surg Gynec Obstet* 79 240
Elman R Arneson N and Graham E A (1929) *Arch Surg Chicago* 19 943
— (1933) *Surg Gynec Obstet* 62 291
— (1939) *Amer J digest Dis* 6 474
Entemnan C Chaikoff I L and Montgomery M L (1944) *J biol Chem* 155 573
Farrell J I and Ivy A C (1926) *Amer J Physiol* 78 325
Fauley G B Freeman S Ivy A C Atkinson A J and Wigodsky H S (1941) *Arch intern Med* 67 563
Fisher N F (1924) *Ibid* 67 634
Frazer A C Schulman J H and Stewart H C (1944) *J Physiol* 103 306
— and Sammons H G (1945) *Biochem J* 39 122
Gaensler E A McGowan J M and Henderson F F (1948) *Surgery* 23 211
Gambill E E (1947) *Proc Mayo Clin* 22 537
— Comfort M W and Baggenstoss A H (1948) *Gastroenterology* 11 1
Garrod A E (1920) *Lancet* 1 749
Gottesman J Casten D and Beller A J (1943) *J Amer med Ass* 123 892
Gray S H and Somogyi M (1937) *Proc Soc exp Biol N Y* 36 253
Greengard H Grossman M I Woolley J R and Ivy A C (1944) *Science* 99 350
Gross J B Comfort M W Mathieson D R and Power M H (1951) *Proc Mayo Clin* 26 81
Grossman M I (1950) *Physiol Rev* 30 33
Halsted W S (1901) *Johns Hopk Hosp Bull* 12 179
Harms E (1927) *Arch klin Chir* 147 637
Harper A A and Vass C C N (1941) *J Physiol* 99 415
— and Raper H S (1943) *Ibid* 102 115
— and Mackay I F S (1948) *Ibid* 107 89
Herring P T and Simpson S (1909) *Quart J exp Physiol* 2 99
Howard J M Krehl Smith A and Peters J J (1949) *Surgery* 26 161
Huggins C and Russell P S (1948) *Ann Surg* 128 668
Ivy A C Farrell J I and Lueth H G (1927) *Amer J Physiol* 82 27
Johnson T A and Bockus H L (1940) *Arch intern Med* 66 62
— (1950) *Postgraduate Gastroenterology* p 310 Ed by H L Bockus Philadelphia Saunders
Jones C M Culver D J Drummey G D and Ryan A E (1948) *Ann intern Med* 29 1
Jones R (1943) *Amer J med Sci* 205 277
Kamer J H van de Huinink H and Weyers H A (1949) *J biol Chem* 177 345
Knight W A Muether R C and Sommer A J (1949) *Gastroenterology* 12 34
Lagerlof H (1939) *Quart J Med* 8 115
— (1942) *Acta med Scand Suppl* 128
— (1945) *Ibid* 120 407
— (1947) *Ibid Suppl* 196 399
Lagerlof J (1947) *Acta chir Scand* 95 297
Lake M (1947) *Amer J Med* 3 18
Lewison E F (1940) *Arch Surg Chicago* 41 1008
Lim R K S Matheson A R and Schlapp W (1923) *Quar J exp Physiol* 13 333
Lionells T Ficarra B J and Ryan L H (1944) *Arch Surg Chicago* 48 137
Lopusniak M and Bockus M (1950) *Gastroenterology* 16 306
McGowan J M Butsch W L and Walters W (1936) *J Amer med Ass* 106 2227
McHenry E W and Patterson J M (1944) *Physiol Rev* 24 128
McWhorter G L (1932) *Arch Surg Chicago* 25 958
Malet Guy P Jeanjean R and Servettaz P (1945) *Lyon chir* 40 293
Mann F C and Giordano A S (1923) *Arch Surg Chicago* 6 1
Marion P (1945) *Lyon chir* 40 315
Mellanby J (1925) *J Physiol* 60 85
Mering J von and Minkowski O (1890) *Arch exp Path Pharmak* 26 371
Minkowski O (1889) *Sem méd Paris* 9 175
— and Mering J von (1889) *Ibid* 9 351
Myhre J Nesbitt S and Hurly J T (1949) *Gastroenterology* 13 127
Opie E L (1901) *Johns Hopk Hosp Bull* 12 182

Pavlov I P (1902) *The work of the digestive glands* English translation by W H Thompson London Griffiths
Pollard H M Miller L and Brewer W A (1942) *Amer J digest Dis* 9 68
Popielski L B (1896) Quoted by Pavlov I P (1902)
Popper H L (1942) *Amer J digest Dis* 9 186
— Olson W H and Necheles H (1943) *Surg Gynec Obstet* 77 471
— and Necheles H (1943) *Gastroenterology* 1 490
Pratt J H Brugsch H G and Rostler A E (1940) *Trans Ass Amer Phys* 60 154
Raffensperger E C (1950) *Postgraduate Gastro enterology* p 315 Ed by H L Bockus Philadelphia Saunders
Ray B S and Console A D (1949) *Surg Gynec Obstet* 89 1
Rich A R and Duff G L (1936) *Johns Hopk Hosp Bull* 58 212
Richman A and Colp R (1950) *Ann Surg* 131 145
Somogyi M (1931–2) *Proc Soc exp Biol N Y* 29 426
— (1932) *J biol Chem* 97 86
— (1934–5) *Proc Soc exp Biol N Y* 32 538
— (1938) *J biol Chem* 125 399
— (1941) *Arch intern Med* 67 665
Takats G de and Walter L E (1947) *Surg Gynec Obstet* 85 742
— — and Lasner J (1950) *Ann Surg* 131 44
Tonkich A (1924) *Pflug Arch ges Physiol* 206 525
Turner G Grey (1920) *Brit J Surg* 7 394
Utendorfer R W and Bergh G S (1948) *Gastroenterology* 11 341
Voegtlin W L Greengard M and Ivy A C (1934) *Amer J Physiol* 110 198
Voet R (1943) *Étude clinique et radiologique des syndromes pancréatiques* Courtrai Jos Vermant
Wang C C and Grossman M I (1950) Quoted Grossman M I (1950)
Waugh J M (1947) *Proc Mayo Clin* 22 558
Wertheimer E and Lepage L (1901a) *J Physiol Path gén* 3 355
— — (1901b) *Ibid* 3 363
— — (1901c) *Ibid* 3 689
— — (1901d) *Ibid* 3 70°
Whipple A O (1946) *Arch Surg Chicago* 124 991
Wolfer J A (1931) *Surg Gynec Obstet* 53 433
— (1937) *Surgery* 1 928
Wollager E E Comfort M W and Osterbe g A E (1947) *Gastroenterology* 9 273

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